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AIR POLLUTION: AIR QUALITY CRITERIA FOR CARBON MONOXIDE

NATO Committee on the Challenges of Modern Society

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AIR QUALITY CRITERIA FOR CARBON MONOXIDE

A Report by the Expert Panel
on
Air Quality Criteria

Committee on Challenges of Modern Society
North Atlantic Treaty Organization

June 1972

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FOREWORD

The material presented in this document represents an effort by the Expert Panel for Air Quality Criteria, Committee on the Challenges of Modern Society, NATO, to compile a compendium of information using the United States Air Quality Criteria for Carbon Monoxide as a basic document on the effects of carbon monoxide (CO) in the ambient air on man and vegetation.

Air quality criteria are an expression of the scientific knowledge of the relationship between various concentrations of pollutants in the air and their adverse effects on man and his environment. Air quality criteria are descriptive; that is, they describe the effects that have been observed to occur when the concentration of a pollutant in the ambient air has reached or exceeded a specific level for a specific time period. In the development of criteria, many factors have to be evaluated. The chemical and physical characteristics must be considered, along with exposure time and conditions of the environment. The criteria must also include consideration of the contributions of all such variables to the effects of air pollution on human health, agriculture, materials, visibility, and climate. Further, the individual characteristics of the receptor must be taken into account.

This document focuses on carbon monoxide as it is found in the ambient air; therefore, literature on extremely high levels of CO has not been extensively cited. The occurrence, properties, and fate of atmospheric CO and the principles of formation and control are reviewed in the earlier chapters; these are followed by a discussion of estimation of CO emissions and measurement of atmospheric CO. The effects of CO

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are considered in relation to vegetation, animals, and man. Reviews of both toxicological and epidemiological studies are presented.

Recent interest and activity on the part of the public, governmental, scientific, academic, and industrial sectors of our communities have stimulated research on the effects of pollution on man and his environment. The result is an ever-increasing body of knowledge that must be analyzed, interpreted, and finally expressed as information supporting or refuting suggested criteria. The assimilation of this new knowledge is not a task that can be undertaken by a small body of men--such as a committee of this nature. Rather, the responsibility for ensuring that criteria continually reflect the most significant information available rests with those same sectors of our communities that have inspired all of us to strive to improve our environment--the public, the government, the scientific, the academic, and the industrial sectors.

The Panel encourages and welcomes new data, comments, and constructive criticism of this document. We suggest that a procedure be established whereby this document and documents to follow can be revised and updated periodically.

For the Expert Panel,
F. G. Hueter, Ph.D., Chairman

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The Chairman of the Expert Panel on Air Quality Criteria wishes to acknowledge the scientists participating from pilot, co-pilot, and observer countries and the many other persons who assisted in the preparation of this document.

The working group, which performed diligently through the course of this effort, receives the highest praise. The group members were:

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F. G. Hueter, Ph.D.
Panel Chairman

TABLE OF CONTENTS

Chapter — Page

- LIST OF FIGURES ... xiii
- LIST OF TABLES ... xvi
- 1. OCCURRENCE, PROPERTIES, AND FATE OF ATMOSPHERIC CARBON MONOXIDE ... 1-1
  - A. INTRODUCTION ... 1-1
  - B. CARBON MONOXIDE IN HISTORY ... 1-1
  - C. OCCURRENCE ... 1-2
    - 1. Technological Sources ... 1-3
    - 2. Natural Sources ... 1-3
      - a. Nonbiological ... 1-3
      - b. Biological ... 1-3
  - D. PROPERTIES AND GASEOUS REACTIONS OF CARBON MONOXIDE ... 1-4
    - 1. Physical Properties ... 1-4
    - 2. Gaseous Chemical Reactions of Carbon Monoxide ... 1-4
      - a. Lower Atmospheric Reactions ... 1-4
      - b. Upper Atmospheric Reactions ... 1-6
  - E. BACKGROUND LEVELS AND FATE OF ATMOSPHERIC CARBON MONOXIDE ... 1-7
    - 1. Background Levels and Estimated Mean Lifetime of Carbon Monoxide ... 1-7
    - 2. Possible Processes for CO Removal ... 1-8
      - a. Oxidation in the Stratosphere ... 1-9
      - b. Biological Removal ... 1-9
      - c. Biochemical Removal ... 1-11
      - d. Adsorption in Oceans ... 1-11
      - e. Adsorption on Surfaces ... 1-11
  - F. SUMMARY ... 1-12
  - G. REFERENCES FOR CHAPTER 1 ... 1-13
- 2. PRINCIPLES OF FORMATION AND CONTROL OF CARBON MONOXIDE ... 2-1
  - A. INTRODUCTION ... 2-1
  - B. FORMATION OF CARBON MONOXIDE BY COMBUSTION ... 2-1
    - 1. General Combustion Processes ... 2-1
    - 2. Internal Combustion Engines ... 2-2
    - 3. Stationary Combustion Systems ... 2-4
  - C. SUMMARY ... 2-5
  - D. REFERENCES FOR CHAPTER 2 ... 2-5
- 3. ESTIMATION OF CARBON MONOXIDE EMISSIONS ... 3-1
  - A. INTRODUCTION ... 3-1
  - B. RECENT CARBON MONOXIDE EMISSION LEVELS ... 3-1
    - 1. National Emission Levels ... 3-1
    - 2. Regional Emission Levels ... 3-2
  - C. EMISSIONS AND EMISSION FACTORS BY SOURCE TYPE ... 3-2
    - 1. Mobile Combustion Sources ... 3-2
      - a. Motor Vehicles ... 3-2
      - b. Aircraft ... 3-11
      - c. Other Nonhighway Mobile Sources ... 3-14
    - 2. Carbon Monoxide from Combustion for Power and Heat ... 3-15
    - 3. Industrial Processes Producing Carbon Monoxide ... 3-16
    - 4. Solid-Waste Combustion ... 3-18
    - 5. Miscellaneous combustion ... 3-18
  - D. PROJECTIONS OF CARBON MONOXIDE EMISSION LEVELS ... 3-19
  - E. SUMMARY ... 3-20
  - F. REFERENCES FOR CHAPTER 3 ... 3-21

4. MEASUREMENT OF CARBON MONOXIDE CONCENTRATIONS IN AMBIENT AIR... 4-1
  A. INTRODUCTION........ 4-1
  B. PREPARATION OF CARBON MONOXIDE GAS STANDARDS........ 4-2
    1. Volumetric Gas Dilution Techniques........ 4-2
    2. Gravimetric Methods for Standardizing Carbon Monoxide Gas Mixtures........ 4-2
    3. Chemical Assay of Carbon Monoxide Gas Standards........ 4-3
  C. MEASURING CARBON MONOXIDE IN ATMOSPHERE........ 4-4
    1. Continuous Measurement of Carbon Monoxide........ 4-4
      a. Definitions of Terms Describing Instrument Performance........ 4-4
      b. Nondispersive Infrared Analyzers........ 4-5
      c. Electrochemical Analyzers........ 4-9
        (1) Galvanic Analyzer........ 4-9
        (2) Coulometric Analyzer........ 4-9
      d. Mercury Vapor Analyzer........ 4-10
      e. Gas Chromatographic Analyzer........ 4-11
      f. Catalytic Analysis........ 4-11
    2. Intermittent Analysis........ 4-12
      a. Collection of Spot or Integrated Samples........ 4-12
      b. Nondispersive Infrared Analysis........ 4-12
      c. Infrared Spectrophotometric Analysis........ 4-12
      d. Gas Chromatographic Analysis........ 4-13
      e. Colorimetric Analysis........ 4-13
        (1) Colored Silver Sol Method........ 4-13
        (2) U.S. National Bureau of Standards Colorimetric Indicating Gel........ 4-14
        (3) Length-of-Stain Indicator Tube........ 4-14
  D. SUMMARY........ 4-15
  E. REFERENCES FOR CHAPTER 4........ 4-17
5. ATMOSPHERIC CARBON MONOXIDE CONCENTRATIONS........ 5-1
  A. INTRODUCTION........ 5-1
  B. TEMPORAL VARIATIONS IN CARBON MONOXIDE CONCENTRATIONS........ 5-1
    1. Diurnal Patterns........ 5-1
    2. Seasonal Patterns........ 5-6
    3. Annual Variations........ 5-6
  C. EFFECT OF METEOROLOGICAL FACTORS 5-9
  D. OBSERVED URBAN CARBON MONOXIDE CONCENTRATIONS........ 5-12
    1. Sources of Data........ 5-12
    2. Techniques of Data Analysis........ 5-12
      a. Introduction........ 5-12
      b. Averaging Time........ 5-13
      c. Frequency Distribution........ 5-14
      d. An Air Quality Model........ 5-16
    3. Special Carbon Monoxide Exposure Situations........ 5-18
      a. Variations With Type of Vehicle Traffic........ 5-18
      b. Car Passenger Exposure to Carbon Monoxide........ 5-20
      c. Severe Carbon Monoxide Exposure Locations........ 5-22
      d. Indoor Levels of Carbon Monoxide........ 5-23
      e. Projected Future Trends........ 5-23
  E. METEOROLOGICAL DIFFUSION MODELS........ 5-25
  F. SUMMARY........ 5-28
  G. REFERENCES FOR CHAPTER 5........ 5-29

6. EFFECTS OF CARBON MONOXIDE ON PLANTS AND CERTAIN MICROORGANISMS.......... 6-1
  A. GENERAL DISCUSSION.......... 6-1
  B. SUMMARY.......... 6-3
  C. REFERENCES FOR CHAPTER 6.......... 6-4
7. TOXICOLOGICAL APPRAISAL OF CARBON MONOXIDE.......... 7-1
  A. INTRODUCTION.......... 7-1
  B. THEORETICAL CONSIDERATIONS.......... 7-2
  C. MEASUREMENT OF CARBOXYHEMOGLOBIN IN BLOOD.......... 7-5
    1. Nondestructive Methods.......... 7-7
      a. Ratio Methods.......... 7-8
      b. Spectrophotometric Extinction Measurements of Isolated COHb.......... 7-10
    2. Destructive Methods.......... 7-11
      a. Carbon Monoxide Detector Tubes.......... 7-11
      b. Reduction Methods.......... 7-11
      c. Monometric and Volumetric Methods.......... 7-12
      d. Spectrophotometric Determination of Released CO by NDIR (Nondispersive Infrared) Method.......... 7-12
      e. Gas-Phase Chromatography.......... 7-13
      f. Determination of Total Hemoglobin.......... 7-13
    3. Equilibrium Methods - Analysis of Expired Air.......... 7-14
    4. Discussion.......... 7-14
  D. UPTAKE OF CARBON MONOXIDE BY HUMANS.......... 7-15
  E. EFFECT OF CARBON MONOXIDE UPON THE CENTRAL NERVOUS SYSTEM.......... 7-26
    1. Animal Data.......... 7-26
      a. Electroencepholographic and Cerebromorphological Findings.......... 7-26
      b. Behavioral Changes.......... 7-27
    2. Human Data.......... 7-33
    3. Discussion.......... 7-49
  F. EFFECTS OF CARBON MONOXIDE ON CARDIOVASCULAR SYSTEM.......... 7-51
    1. Animal Data.......... 7-52
    2. Human Data.......... 7-57
  G. NONHEMOGLOBIN ABSORPTIVE SYSTEMS.......... 7-68
    1. Myoglobin.......... 7-68
    2. Cytochrome Oxidases.......... 7-73
  H. EFFECTS OF CARBON MONOXIDE UNDER HYPOBARIC AND HYPERBARIC CONDITIONS.......... 7-76
    1. High Altitude.......... 7-76
    2. Hyperbaric Conditions.......... 7-83
  I. ADAPTATION.......... 7-84
  J. ENDOGENOUS FORMATION OF CARBON MONOXIDE.......... 7-87
  K. SUMMARY.......... 7-91
  L. REFERENCES FOR CHAPTER 7.......... 7-101
8. EPIDEMIOLOGICAL APPRAISAL OF CARBON MONOXIDE.......... 8-1
  A. INTRODUCTION.......... 8-1
  B. SOURCES AND MAGNITUDE OF EXPOSURE TO CARBON MONOXIDE.......... 8-2
    1. Community and Residential Exposures.......... 8-3
    2. Occupational Exposures.......... 8-4
    3. Cigarette, Pipe, and Cigar Smoke.......... 8-14

C. DEFINITION OF SENSITIVE GROUPS............................ 8-15
D. STUDIES AND INTERPRETATION................................. 8-17
    1. Mortality Studies...................................... 8-17
    2. Morbidity Studies...................................... 8-27
    3. Possible Relevance of Carbon Monoxide Exposure to Motor Vehicle Accidents..................................... 8-29
E. SUMMARY.. 8-31
F. REFERENCES FOR CHAPTER 8................................... 8-34
APPENDIX. CONVERSION BETWEEN VOLUME AND MASS UNITS OF CONCENTRATION.. A-1

LIST OF FIGURES

Figure Page

2-1 Effect of Air-Fuel Ratio on Exhaust Gas Carbon Monoxide Concentrations from Three Internal Combustion Test Engines........ 2-4
3-1 Carbon Monoxide Emissions by Source Category for Various U.S. Metropolitan Areas in 1968.. 3-3
3-2 Effect of Average Route Speed on Carbon Monoxide Emission by Weight.. 3-9
3-3 Carbon Monoxide Emissions by Individual Vehicles, Los Angeles.. 3-10
3-4 Relationship Between Average Vehicle Speed and Carbon Monoxide, Hydrocarbon, and Nitrogen Oxide Concentrations in Auto Exhaust... 3-12
3-5 Relationship Between Average Vehicle Speed and Carbon Monoxide, Hydrocarbon, and Nitrogen Oxide Emission Factors (g/hr)........ 3-12
3-6 Relationship Between Average Vehicle Speed and Carbon Monoxide, Hydrocarbon, and Nitrogen Oxide Emission Factors (g/km)........ 3-13
4-1 Typical Nondispersive Infrared Analyzer Response to Water Vapor.. 4-7
5-1 Diurnal Variations in Mean Carbon Monoxide Levels on Weekdays in Detroit.. 5-2
5-2 Hourly Average Carbon Monoxide Concentrations and Traffic Count in Midtown Manhattan, New York City...................... 5-3
5-3 Average Diurnal Concentration of Carbon Monoxide in Wiesbaden, Germany... 5-4
5-4 Correlation of Carbon Monoxide Concentration and Traffic Density.. 5-5
5-5 Trends in Carbon Monoxide Concentrations in Winter and Summer Half-years in Frankfort/Main, Germany.................. 5-8
5-6 Effect of Wind Speeds <2 m/sec and >2 m/sec on Carbon Monoxide Concentrations at Different Heights Above A Downtown "Canyon" Street.. 5-11
5-7 Maximum Annual 8-Hour-Averaging-Time Concentrations of Carbon Monoxide Expected at Various Types of Sites............ 5-20
7-1 Oxyhemoglobin (O_2Hb) Dissociation Curves of Human Blood Containing Varying Amounts of Carboxyhemoglobin (COHb), Calculated from Observed Oxygen Dissociation Curve of Carbon Monoxide-Free Blood...................................... 7-4
7-2 Effect of Carbon Monoxide Administration on Arterial Oxygen Tension, Compared With Oxygen Dissociation Curves in Figure 7-1, Based on Data in Table 7-1................................ 7-7
7-3 Uptake of Carbon Monoxide at Various Concentrations and Rates of Ventilation... 7-16
7-4 Average Values of Percent Carboxyhemoglobin in Seven Nonsmokers Exposed to 35 mg/m^3 Carbon Monoxide................. 7-18
7-5 Diagramatic Summary of Current Concepts Regarding Variables That Influence Body CO Stores................................. 7-20

Figure | Page

7-6 Comparision of Carboxyhemoglobin Levels Predicted by Three Empirical Formulas and a Theoretical Model................ 7-22
7-7 Comparision of Carboxyhemoglobin Levels Predicted by Three Empirical Formulas and a Theoretical Model Over Long Exposure Times... 7-23
7-8 Comparision of Equilibrium Values of Carboxyhemoglobin for Arbitrarily chosen Exposure Durations, calculated by the California State Department of Health's Formula and the Theoretical Model... 7-24
7-9 Effect of Carbon Monoxide on Mean Differentially Reinforced Response Rate in Rats... 7-28
7-10 Effects of Small Concentrations of COHb on Certain Psychomotor Tests.. 7-36
7-11 Mean Percent Correct Responses (± One Standard Deviation) to 1,000-Hertz Tone by 18 Human Subjects During Exposure to Carbon Monoxide.. 7-38
7-12 Time After Initial Exposure to Each Concentration of Carbon Monoxide at Which Mean Correct Response Fell Two Standard Deviations From Mean Correct Response in Absence of Carbon Monoxide.. 7-39
7-13 Relation Between Carboxyhemoglobin and Visual Threshold.... 7-49
7-14 Myocardial Metabolic Measurements in Three Representative Patients Before and After Carbon Monoxide Inhalation....... 7-64
7-15 Carboxyhemoglobin Concentration in Blood and Carbon Monoxide Partial Pressure in Tissue (i.p.) of Rabbits, Rats, and Guinea Pigs Breathing 0.496 mm Hg Carbon Monoxide (805 mg/m^3 or 700 ppm). Average Values Obtained After Diffusion Equilibrium Was Reached.. 7-69
8-1 Carbon Monoxide Levels of Environmental Air and of Expired Air of Smoker and Nonsmoker, Los Angeles and Pasadena, August 1962.. 8-4
8-2 Carbon Monoxide Levels of Environmental Air Carboxyhemoglobin Levels of Smoker and Nonsmoker, Los Angeles County, 1963...... 8-5
8-3 Distribution of Carboxyhemoglobin Among Individuals Involved in Traffic Accidents... 8-10
8-4 Carboxyhemoglobin Levels of Policemen Who Smoke Before and 5 Hours After Exposure to Between 12 and 23 mg/m^3 (10 and 12 ppm) Carbon Monoxide, Paris, 1963................................ 8-11
8-5 Carboxyhemoglobin Levels of Policemen Who do not Smoke Before and 5 Hours After Exposure to Between 12 and 23 mg/m^3 (10 and 12 ppm) Carbon Monoxide, Paris, 1963.......................... 8-12
8-6 Distribution of Expired - Air Carbon Monoxide, According to Smoking History, and Corrected for Ambient - Air Carbon Monoxide... 8-16
8-7 Percentage of Hemoglobin Saturated With Carbon Monoxide in Cord and Maternal Blood Specimens of Smokers and Nonsmokers........ 8-18
8-8 Comparison of Maximum Concentrations of Oxidant and Carbon Monoxide, Maximum Temperature, and Daily Death Rate for Cardiac and Respiratory Causes, Los Angeles County, 1956-1958........ 8-20
8-9 Fourier Curves Fitted to Data in Figure 8-8................. 8-21

Figure Page

8-10 Carboxyhemoglobin Levels of Coroner's Cases, by Smoking Status and Atmospheric Carbon Monoxide Concentrations, Los Angeles County, 1961.. 8-22

8-11 Carboxyhemoglobin Levels in Myocardial Infarction Deaths and in Other Cardiovascular Disease Deaths, Los Angeles County, 1961.. 8-23

8-12 Cumulative Distribution of Blood Carbon Monoxide Concentrations, Based on 5-year Study of Car Drivers, Workmen With Carbon Monoxide Exposure, and Private Individuals Suspected of Accidental Carbon Monoxide Exposure..................... 8-30

LIST OF TABLES

Table		Page
1-1	Physical Properties of Carbon Monoxide	1-5
3-1	Carbon Monoxide Emission Estimates By Source Category for the United States, 1969	3-5
3-2	Carbon Monoxide Emission Estimates by Source Category for the Federal Republic of Germany, 1969	3-6
3-3	United States Carbon Monoxide Emission Estimates, 1969	3-7
5-1	Correlation Coefficients between Traffic Density and CO Concentration at Six Heights	5-6
5-2	Carbon Monoxide Concentration at CAMP Sites, by Averaging Time and Frequency, 1962 through 1968	5-7
5-3	In-Traffic 20- to 30-Minute Carbon Monoxide Exposures for Various Driving Routes	5-21
7-1	Blood and Gas Studies (Averages of Two Measurements Taken 30 Minutes Apart) After Administration of Carbon Monoxide and Air Until Attainment of Carboxyhemoglobin Equilibrium	7-6
7-2	Results of Physiological and Psychological Tests on Subjects Exposed to 345 mg/m^3 (300 ppm) CO	7-34
7-3	Effects of Varying CO Exposure on Visual Performance	7-46
7-4	Percent Change in Blood Values of Individual Dogs in Response to 58 mg/m^3 (50 ppm) CO Inhalation Daily for 3 Months	7-54
7-5	Hemodynamic and Respiratory Responses of Five Subjects to CO Inhalation	7-58
7-6	Systemic Cardiorespiratory Measurements in 26 Subjects Before and After CO Inhalation	7-60
7-7	Myocardial Metabolic Measurements in 11 Subjects Before and After CO Inhalation	7-62
7-8	Effect of CO on Alveolar-Arterial Oxygen Difference (A-aDO$_2$ In Nine Subjects After Exposure Sufficient to Increase COHb About 10 Percent	7-66
7-9	Extravascular CO Capacities, Half-Times, and Equilibrium Times for Transfer of CO From Intravascular Pool to Extravascular Pool, and Levels of Blood COHb at End of Transfer	7-72
7-10	Average Data for Eight Subjects (Divided Into Two Groups of Four) to Compare Effects of CO and High Altitudes on Various Physiological Parameters	7-79
7-11	Summary of Effects of Carbon Monoxide in Animals	7-93
7-12	Summary of Effects of Carbon Monoxide in Humans	7-95
8-1	COHb Levels of Smokers and Nonsmokers in Exposed and Control Groups	8-7
8-2	Change in Expired-Air Carbon Monoxide Levels During Work in Exposed and Control Border Employees	8-8
8-3	Frequency Distribution of CO Blood Analyses of Individuals Involved in Traffic Accidents	8-10
8-4	COHb Levels of 108 Smokers and 92 Nonsmokers Before Work	8-14

8-5 Proportion of Smokers and Median Values of Expired CO among Longshoremen 8-15
8-6 COHb Levels for Cardiovascular Disease Categories by Age, Smoking Habits, and Sex, Los Angeles County, 1961.......... 8-24
8-7 Relationship between Number of Hospital Admissions for Myocardial Infarction, Myocardial Infarction Case Fatality Rates, and Ambient CO Levels by Day of Week, Los Angeles County, 1958.. 8-26

CHAPTER 1.

OCCURRENCE, PROPERTIES, AND FATE OF ATMOSPHERIC CARBON MONOXIDE

A. INTRODUCTION

Carbon monoxide (CO) is one of the most widely distributed and commonly occurring air pollutants. Total emissions of CO to the atmosphere exceed those of all other pollutants combined.

Carbon monoxide is produced by the incomplete combustion of carbonaceous materials in motor vehicles, space heating, and industrial processing. Natural sources, which may produce CO on the same order of magnitude as man-made sources, have also been identified. The most important natural CO source is the upper layers of oceans and lakes where CO is produced by algae (1).

Man-made sources that emit carbon monoxide are usually located in urban areas. Natural sources, on the other hand, are widespread. The influence of naturally produced CO on the CO concentrations in air over cities is negligible, but may be very important in regard to background CO and the mean residence time of CO in the atmosphere.

This document explores the fundamental knowledge about CO in the context of its role as an air pollutant; there are many other aspects of CO that are of collateral interest. In addition to the references given in this document pertaining to CO, a bibliography (2) compiled in 1966 gives sources of further information.

B. CARBON MONOXIDE IN HISTORY

Human experience with CO probably began during prehistoric times when man first discovered fire. Carbon monoxide poisoning, which has been traced through Greek and Roman literature, has been closely associated with the history of mankind.

Materials used for making fire in prehistoric times were probably wood, grasses, and other organic matter. Lewin (3) cites many cases of CO poisoning caused by the incomplete combustion of such fuels. He also includes references to the effects of CO on the health of man in the writings of Greek physicians of the third century.

With the increased use of coal for domestic heating in the fifteenth century, CO poisoning increased greatly. This increase was caused by inhalation of CO formed by incomplete combustion in the heating of homes, and by the exposure of men in mines where the deadly "white damp" was encountered after explosions and mine fires. The introduction of illuminating gas (a mixture of hydrogen, carbon monoxide, methane, and other hydrocarbons) for domestic heating (still used extensively in Europe, but largely replaced by natural gas in the United States) further increased this hazard.

The introduction of the internal combustion engine for transportation and the development of a number of technological processes wherein CO is produced have greatly increased the production of CO and its release to the atmosphere.

Thus over the past few centuries, the problem of dealing with CO has spread from individual dwellings and work environments to include the ambient air in cities. Concern has now broadened from the acute and often lethal effects of high concentrations of the gas to effects that may occur as a result of considerably longer exposures to much lower concentrations.

C. OCCURRENCE

1. Technological Sources

Carbon monoxide is found among the combustion products of organic materials used as fuels. Transportation activities represent the largest source category. Other major technological sources of CO emissions are stationary heat-generating facilities, industrial processes, and solid-waste combustion. Carbon monoxide is also formed in explosions and in the firing of weapons. It occurs in high concentrations in cigarette smoke. The major technological sources of CO are discussed in greater detail in Chapter 3.

2. Natural Sources

a. Nonbiological

Some CO is reported to be produced in volcanos, and some is formed in natural gases (e.g., gases found in coal mines) (4). It has also been reported to be formed during electrical storms (5). Forest fires also make a contribution to atmospheric CO (6). A small amount of CO is formed as a photochemical degradation product of various reactive organic compounds in the process involving the formation of photochemical smog (7,8). Finally, some CO is believed to be formed in the upper atmosphere above 70 kilometers (km) by photodissociation of carbon dioxide (CO_2) (9).

b. Biological

Small quantities of CO are formed by vegetation during seed germination and seedling growth of plants (10), and it has been observed in injured, cut, or dried plants (11). Some CO is found in marsh gases, and it is also formed by certain brown algae (kelps) (12,13). Carbon monoxide concentrations of up to 900 milligrams per cubic meter (mg/m^3) (786 ppm) have been found in the floats of Nereocystis, a familiar kelp or seaweed (14). Mature leaves of green plants have been shown to produce CO (11). Microorganisms also have been shown to produce CO from plant flavonoids (15).

Carbon-monoxide-producing colonies of marine hydrozoan jellyfish (siphonophores) are widespread and make up a large portion of the plankton in the warmer oceans of the world (16,17). Carbon monoxide is also produced in the float cells of the surface-dwelling Physalia physalis (Portuguese Man-of-War) (18).

The high supersaturation of carbon monoxide in the upper layers of the oceans can be explained by the CO production of microorganisms, especially bacteria and algae (19), which has been confirmed by experiments in the laboratory (20). Rough estimates indicate that the quantity of CO produced by this natural source and that produced by man-made sources is of the same order of magnitude.

Another example of biological CO is endogenous CO, which is produced in measurable quantities in man and animals as a by-product of heme catabolism (21-23). This endogneous CO is produced in larger amounts in hemolytic disease states.

D. PROPERTIES AND GASEOUS REACTIONS OF CARBON MONOXIDE

1. Physical Properties

Carbon monoxide is a colorless, odorless, tasteless gas, slightly lighter than air (24). Quite flammable, it burns with a bright blue flame, but does not support combustion.

Physical properties of CO are outlined in Table 1-1.

2. Gaseous Chemical Reactions of Carbon Monoxide

a. Lower Atmospheric Reactions

Under atmospheric conditions there are several reactions that can oxidize CO to CO_2, some of which were proved by Bates and

Table 1-1. PHYSICAL PROPERTIES OF CARBON MONOXIDE

Property	Value
Molecular weight	28.01
Melting point	-207°C
Boiling point	-192°C
Specific gravity relative to air	0.968
Density	
At 0°C, 760 mm Hg	1.25 g/liter
At 25°C, 760 mm Hg	1.15 g/liter
Explosive limits in air	12.5 to 74.2% (volume)
Solubility	
At 0°C, 760 mm Hg	3.54 ml/100 ml water
At 25°C, 760 mm Hg	2.14 ml/100 ml water
Conversion factors	
At 0°C, 760 mm Hg	1 mg/m^3 = 0.800 ppm 1 ppm = 1.250 mg/m^3
At 25°C, 760 mm Hg	1 mg/m^3 = 0.874 ppm 1 ppm = 1.145 mg/m^3

Witherspoon (9). The reaction between CO and molecular oxygen

$$2\ CO + O_2 \longrightarrow 2\ CO_2$$

is possible but not of great enough magnitude to be important. Both dry and moist experimental mixtures of CO and O_2 have remained unchanged after 7 years of exposure to sunlight (25). The rate of oxidation of CO by O_2 can be increased by catalysts, however. For example, CO can be oxidized at room temperature by hopcalite - a mixture of manganese, copper oxide, and palladium. This means of reaction is probably not of great importance in the atmosphere.

Other possible atmospheric reactions for the oxidation of CO to CO_2 are shown below:

$$CO + O_2 \longrightarrow CO_2 + O$$

$$CO + H_2O \longrightarrow CO_2 + H_2$$

$$CO + O_3 \longrightarrow CO_2 + O_2$$

$$CO + NO_2 \longrightarrow CO_2 + NO$$

Because all these reactions are exothermic, they are of great importance only at higher temperatures. The reaction rates at atmospheric temperatures are so low that these reactions are not important for the conversion of CO to CO_2 in the atmosphere.

Another possible means of oxidizing CO is by reaction with atomic oxygen. This reaction is not important because of the rapid combination of atomic oxygen with O_2 (26).

The reaction between CO and OH

$$CO + OH \longrightarrow CO_2 + H$$

is rapid enough to oxidize large quantities of CO even at stratospheric temperatures (27). It is virtually impossible, however, to measure the extremely low OH concentrations in the stratosphere.

Nevertheless, CO oxidation by OH is more than speculative. Hydroxyl radicals are formed by the reaction between H_2O and excited oxygen atoms, which themselves are formed by the photolysis of ozone. The steps of these reactions are known well enough, through laboratory experiments, to estimate the OH production that results from this mechanism (28).

b. Upper Atmospheric Reactions

Ultraviolet radiation (<2000 Å) dissociates CO_2 into CO and O. The dissociation occurs at altitudes higher than 30 km (29) and is comparable with the dissociation of water vapor. Carbon monoxide is also produced by the photochemical oxidation of CH_4 (28). In addition, OH radicals are found in the upper atmosphere (30), which suggests that oxidation of CO by OH occurs.

E. BACKGROUND LEVELS AND FATE OF ATMOSPHERIC CARBON MONOXID[illegible]

1. Background Levels and Estimated Mean Lifetime of Carbon Monoxide

The amount of CO measurable in relatively unpolluted (clean) air is small. Junge has estimated the background level of CO in the lower atmosphere to be in the range of 0.01 to 0.2 mg/m^3 (0.01 to 0.2 ppm) (31). With the use of spectral techniques, studies of background levels of CO conducted at Mt. Wilson, California; Ottawa, Canada; Jungfraujoch, Switzerland; and Columbus, Ohio, confirmed that such levels average about 0.1 mg/m^3 (0.1 ppm) (32-34).

Robbins et al. found CO concentrations between 0.06 and 1.2 mg/m^3 (0.05 and 1.0 ppm) in maritime air masses over California (35); they measured concentrations as low as 0.029 mg/m^3 (0.025 ppm) over the northern Pacific and 0.023 mg/m^3 (0.020 ppm) over the southern Pacific. The same researchers found CO values of 0.058 to 0.748 mg/m^3 (0.050 to 0.65 ppm) and 0.063 to 0.299 mg/m^3 (0.055 to 0.260 ppm) over north Greenland and Alaska, respectively. All measurements showed fluctuations of CO concentrations with time. Robbins et al. attributed the fluctuations over Greenland and Alaska to the man-made production of CO over the United States. The fluctuations over the southern Pacific, however, remain unexplained.

On the other hand, Seiler and Junge (36) found CO values of 0.21 mg/m^3 (0.18 ppm) and 0.057 mg/m^3 (0.05 ppm) over the northern Atlantic and southern Atlantic, respectively. The concentrations fluctuated between

0.18 and 0.23 mg/m^3 (0.16 and 0.20 ppm) over the northern Atlantic. Seiler (36), however, found no fluctuations in CO levels over the southern Pacific and southern Atlantic.

It appears that there are two different background CO concentrations for northern and southern hemispheric air; these concentrations are estimated to be 0.21 and 0.06 mg/m^3 (0.18 and 0.05 ppm), respectively. These hemispheric air masses are separated over the Atlantic at the intertropical convergence zone (ITC) at sea level. In the upper troposphere (approximately 10 km), Seiler could find no difference in CO concentrations between 50 degrees north and 25 degrees south latitude. The mean value in the higher troposphere was from 0.15 to 0.16 mg/m^3 (0.13 to 0.14 ppm).

The mean residence time of CO in the atmosphere is not definitely known. Through radioactive techniques, the average residence time was estimated to be 0.2 year (1). The constancy of the CO concentration with time over the oceans shows a longer residence time (approximately 1 year).

2. Possible Processes for CO Removal

The average CO concentration in the atmosphere is about 0.15 mg/m^3 (0.13 ppm). If no sinks (processes by which CO is removed from the atmosphere) for CO existed in the atmosphere, the average CO concentration would be expected to increase by about 0.03 mg/m^3 (0.03 ppm) per year as a result of man-made CO production. Because the average CO concentration had not increased over a period of several years, it was known that such sinks did exist. Some of the sinks for atmospheric CO that have been identified in recent years are discussed in the following paragraphs.

a. Oxidation in the Stratosphere

When the tropopause was crossed during several flights on the polar route between Frankfurt and Tokyo, Seiler and Junge (37) found a rapid decrease in the CO mixing ratio above the tropopause. They assumed a reaction between CO and $(OH)^-$ in the stratosphere. The suitability of this assumption was confirmed by theoretical calculations (27,38) that showed 3×10^6 molecules OH/cm^3 to be sufficient to oxidize the CO flux from the troposphere into the stratosphere. In the winter of 1970/71 similar flights were made, and the gradient of CO mixing ratio above the tropopause was measured (39). This sink is not sufficient, however, to compensate for the known sources of CO.

b. Biological Removal

Another possible removal agent of atmospheric CO is plants and microorganisms, in significant numbers, that can metabolize CO. Soil has been found to be a sink for CO in two recent studies. Inman et al. (40) measured the CO reduction over different types of soil. They found that 138 mg/m^3 (120 ppm) CO placed over soil in testboxes was removed within a period of 3 hours. The maximum removal occurred at a soil temperature of 30 °C.

Liebl (41) worked with CO concentrations of 0.23 mg/m^3 (0.2 ppm) and soil temperatures of 10 to 52 °C. He found an average removal rate of 10^{-11} g CO/cm^2-sec at a soil temperature of 20 °C over loam. This study indicates that soil may act as a sink for CO. The global CO removal capacity of soil cannot be estimated on the basis of the above data because of the variety of soil types and temperatures over the world. If one assumes that the above data apply to 20 percent of the global land mass, then soil can account for the removal of 100×10^6 tons of CO per year. The mechanisms of the removal process are not yet known, but it is assumed that microorganisms may be responsible.

It is known that some common specific anaerobic methane-producing soil microorganisms, Methanosarcina barkerii and Methanobacterium formicum, can convert CO into CH_4 in the presence of moisture. This action has been demonstrated in the laboratory by Schnellen (42), who showed that pure cultures of these bacteria convert CO into methane. Schnellen has found that Ms. barkerii is capable of converting CO to CH_4 according to the equation:

$$4\ CO + 2\ H_2O \longrightarrow CH_4 + 3\ CO_2$$

Stephenson (43), however, indicates that CO, in the absence of H_2, reacts with water in these bacteria in two stages as follows:

$$4\ CO + 4\ H_2O \longrightarrow 4\ CO_2 + 4\ H_2$$

and

$$CO_2 + 4\ H_2 \longrightarrow CH_4 + 2\ H_2O.$$

In the presence of H_2, these bacteria convert CO directly into methane and water:

$$CO + 3\ H_2 \longrightarrow CH_4 + H_2O.$$

An aerobic soil bacterium, Bacillus oligocarbophilus (Carboxydomonas oligocarbophila), found in and isolated from arable soil, has also been demonstrated to oxidize CO to CO_2. When cultivated on simple organic media free from other carbon sources, this organism oxidizes CO to CO_2, which is then utilized as a source of energy (44). Another bacterium, Clostridium welchii, when grown in the presence of CO, has been reported to produce lactic acid as a fermentation product (45).

Although these soil bacteria utilize CO in their fermentation or metabolic processes, it is difficult to estimate global destruction rates of

CO on the basis of such laboratory experiments.

Within the biosphere, the process of plant respiration may serve as a potential removal process; however, this concept has not been firmly established, even though it is recognized that plants are scavengers for a wide variety of atmospheric materials. Chapter 6 of this document treats this subject in greater detail.

c. Biochemical Removal (Biochemical Sink).

A potential biochemical removal process for CO is the binding of CO to the porphyrin-type compounds that are widely distributed in plants and animals. In particular, the heme compounds such as hemoglobin, which are analogous to porphyrin compounds found in plants, are known to bind CO. It must be noted, however, that practically all of the CO absorbed by the heme compounds found in man and animals is eventually discharged from the blood, and only a small fraction is retained (46). This type of process in vegetation may have an important potential for scavenging atmospheric CO. Permanent removal from the environment, however, would depend on whether CO subsequently enters into some reaction process to form CO_2 when the porphyrin compound is degraded.

d. Absorption in Oceans (Oceanic Sink).

The oceans, as pointed out above (1, 19), can be considered a source of CO rather than a sink because of the high supersaturation of CO in the upper layers of seawater. The question of whether large inland lakes are a sink or a source has not been satisfactorily assessed at the present time.

e. Adsorption on Surfaces.

Kummler et al. indicate that the gas-phase oxidation of CO by nitrous oxide (N_2O), considered too slow to be of importance in the atmospher is catalyzed in the presence of certain surfaces (such as charcoal, carbon black, and glass) at 300 °C and above (47). These investigators have extrapolated these reported high-temperature reaction rates to 27 °C and consider that such a catalytic reaction is feasible at ambient temperatures. This conclusion is supported by laboratory studies of Gardner and Petrucci (48), wherein the chemisorption of CO on metallic films (such as copper, cobalt, and nickel oxides) at room temperatures was measured by infrared spectroscopy.

The necessary data for evaluation of the catalytic efficiency of common surfaces such as metals, soil, and atmospheric particles are presently unavailable. A paper by Liberti (49) reports the results of analyses of urban particulate matter. Liberti found carbon monoxide concentrations ranging from 10 to 30 μg/g; he indicates that the adsorption of CO by dust may be an important removal mechanism of CO, and that dust could be an important avenue (through deposition) of making CO available to soil microorganisms for subsequent oxidation.

F. SUMMARY

Carbon monoxide, which constitutes the largest single fraction of the pollutants found in urban atmospheres, is produced primarily by the incomplete combustion of organic materials used as fuels for both transportation and space heating; it also results from industrial processes, refuse burning, and agricultural burning.

Although several natural sources of CO of both biological and nonbiological origin have been identified, their influence on the CO concentration in air in cities is considered to be negligible. The CO background concentration of clean, uncontaminated air has been found to be 0.15 to 0.16 mg/m^3 (0.13 to 0.14 ppm) in the northern hemisphere and 0.06 mg/m^3 (0.05 ppm) in the southern hemisphere.

Carbon monoxide is colorless, tasteless, and odorless; although flammable, it does not support combustion. Oxidation reactions which convert CO to CO_2 occur with both oxygen and water vapor in the lower atmosphere, but the rates of these reactions are very slow.

Worldwide emissions of CO from technological sources have been estimated to be more than 1.8×10^{11} kg (200 million tons) annually. In the absence of any removal processes, this large tonnage would be sufficient to raise the background level of CO by 0.03 mg/m^3 (0.03 ppm) per year; yet this background level does not appear to be rising. The mean residence time of atmospheric CO has been estimated to be between 0.2 and 3 years.

Several removal processes are known that explain the constancy of the CO background. The oxidation of CO by OH radicals seems to be the most important sink. Additionally, CO is removed by terrestrial biospheres, through processes such as the metabolic conversion of CO to CO_2 and methane by soil microorganisms; the binding of CO to porphyrin compounds in plants and animals, with subsequent oxidation of the CO to CO_2; and the adsorption and subsequent oxidation of CO on various surfaces. Although the biosphere provides several potential mechanisms involving both land and marine plant and animal communities, the precise mechanism of removal of CO from the atmosphere cannot at present be identified with any certainty. In fact, some of the CO sinks discussed above are highly speculative and may actually contribute CO to, rather than remove it from, the atmosphere.

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CHAPTER 2.

PRINCIPLES OF FORMATION AND CONTROL OF CARBON MONOXIDE

A. INTRODUCTION

Carbon monoxide formation results directly from the incomplete combustion of a gaseous, liquid, or solid carbon-containing fuel; therefore, the CO found in urban air generally has its origin in one of the many combustion processes associated with man's day-to-day activities, industry, and commerce. It is the purpose of this chapter to discuss the general mechanisms of combustion that lead to the formation of CO and the specific involvement of those mechanisms in CO formation in mobile and stationary sources. More detailed information in this area can be found in the references at the end of this chapter (1,2).

B. FORMATION OF CARBON MONOXIDE BY COMBUSTION

1. General Combustion Processes

Incomplete combustion of carbon or carbon-containing compounds creates varying amounts of CO. The chemical and physical processes that occur during this combustion are complex because they depend not only on the type of carbon compound reacting with oxygen, but also on the conditions existing in the combustion chamber. Despite the complexity of the combustion process, certain general principles regarding the formation of CO from the combustion of hydrocarbon fuels are widely accepted.

Gaseous or liquid hydrocarbon fuel reacts with molecular oxygen in a chain of reactions that culminate in the production of CO. Carbon monoxide then reacts with hydroxyl radicals to form carbon dioxide. This second reaction is approximately ten times slower than the first. In coal combustion, the reaction of carbon and oxygen to form CO is also one of the primary reactions, and a large fraction of carbon atoms goes through the monoxide form. Again the reaction of monoxide to dioxide is much slower.

Consideration of this mechanism leads to four basic variables that control the concentration of CO in all combustion of hydrocarbon gases. These variables are oxygen concentration, flame temperature, gas residence time at high temperature, and combustion-chamber turbulence. Oxygen concentration affects the formation of both CO and CO_2 because oxygen is required in the initial reactions with the fuel molecule and in the formation of the hydroxyl radical. As the availability of oxygen increases, more complete conversion of monoxide to dioxide occurs. Flame temperature affects both the formation of monoxide and the conversion of monoxide to dioxide because both reaction rates increase exponentially with increasing temperature. The conversion of CO to CO_2 is also enhanced by longer residence time because conversion is a relatively slow reaction compared to CO formation. Increasing combustion-gas turbulence increases the actual reaction rates by bypassing the relatively slower gaseous diffusion mixing process.

2. Internal Combustion Engines

The two factors that effectively determine total CO emissions from internal combustion engines are the concentration of CO in the exhaust and the volume of exhaust. The exhaust concentration depends mainly on the air-to-fuel (A/F) ratio entering the combustion cylinder; the exhaust volume depends on the power output.

Exhaust concentrations of CO increase with lower (richer) A/F ratios, decrease with higher (leaner) A/F ratios, but remain relatively constant with ratios above the stoichiometric ratio of about 15 to 1 (3). The behavior of gasoline automobile engines before and after the installation of pollutant control devices differs considerably. Depending on the mode of driving, the average uncontrolled engine operates at A/F ratios ranging from about 11 to 1 to a point slightly above the stoichiometric ratio. During the idling mode, at low speeds with light load (such as low-speed cruise), during the full-throttle mode until speed picks up, and during deceleration, the A/F ratio is low in uncontrolled cars, and CO emissions are high. At higher-speed cruise and during moderate acceleration, the reverse is true. Cars with exhaust controls generally remain much closer to stoichiometric A/F ratios in all modes, and thus the CO emissions are kept lower. The relationship between exhaust CO concentration and A/F ratio is shown in Figure 2-1.

The exhaust flow rate increases with increasing engine power output. During idle the flow is minimum; during full throttle it is maximum. At cruise engine conditions (i.e., constant engine speed and power output) the exhaust flow remains constant. The flow increases during engine acceleration.

Correlations between total emissions of CO in pounds per vehicle mile and average route speed (discussed in greater detail in Chapter 3) show a decrease in emissions with increasing average speed (4). During low-speed conditions, (below 32 km/hr or 20 mi/hr) the greater emissions per unit of distance traveled are attributable to an increase in the frequency of acceleration,

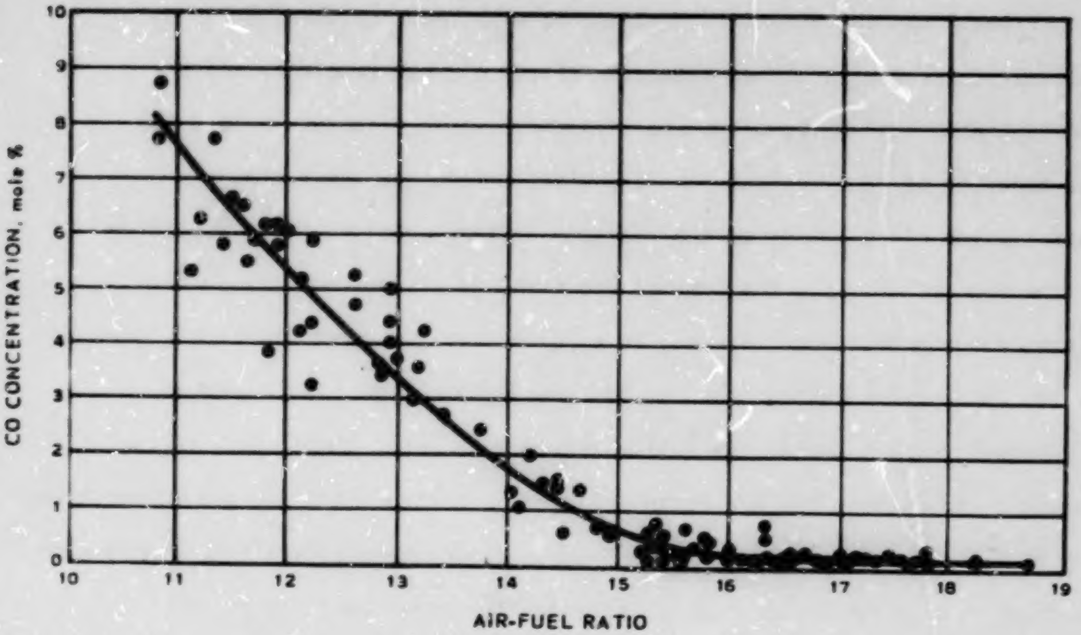

Figure 2-1. Effect of air-fuel ratio on exhaust gas carbon monoxide concentrations from three internal combustion test engines (3).

deceleration, idle stages of the driving cycle, as well as "greater residence time" encountered by the vehicle in heavy traffic.

3. Stationary Combustion Systems

In the design of stationary combustion systems, a high combustion temperature is necessary to achieve high thermal efficiency. This temperature can be achieved at A/F ratios slightly in excess of stoichiometric (5).

Carbon monoxide concentrations in the exhaust gases are influenced primarily by the A/F ratios, the mixing of the reactants, and the residence time within the combustion chamber. At lower than stoichiometric A/F ratios, with complete mixing of the reactants, relatively high CO concentrations occur because of the principles of chemical thermodynamics.

At A/F ratios in excess of stoichiometric, CO concentrations decrease considerably, reaching a minimum at excess A/F ratios of about 20 percent to 30 percent (depending on the fuel used). The practical requirement to achieve a possible high thermal efficiency as well as a requirement of low CO concentrations in the exhaust gas can, therefore, be realized only by good mixing of the reactants, optimum residence time in the combustion chamber, and A/F ratios higher than stoichiometric. Combustor design dictates the minimum CO emissions that can be achieved, and operating practice dictates the actual approach to that minimum.

C. SUMMARY

Carbon monoxide is formed predominantly by incomplete or inefficient combustion. If any of the four variables that control this process are low, CO emissions may be high. These variables are oxygen concentration, flame temperature, gas residence time at high temperature, and combustion-chamber turbulence. In the internal combustion engine, the air/fuel ratio controls the CO concentration in the exhaust, whereas the total volume of exhaust relates to power output. In stationary sources, combustor design and operation determine the CO emissions.

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CHAPTER 3.

ESTIMATION OF CARBON MONOXIDE EMISSIONS

A. INTRODUCTION

The potential for carbon monoxide emissions exists everywhere combustion occurs. Because combustion takes such a multitude of forms, the task of evaluating the relative importance of different CO sources requires considerable variety in methods of estimation. Of the numerous source categories of CO, fuel combustion in mobile sources utilizing the internal combustion engine is the principal source category of CO in the United States (1) and the Federal Republic of Germany (2).

Miscellaneous combustion sources - principally forest fires - and industrial process sources are the second and third largest categories of CO emissions respectively. Disposal of solid wastes, either by open burning or incineration, and stationary fuel combustion are the fourth and fifth largest categories, respectively. A more detailed discussion of the information presented in this chapter may be found in References (3) and (4).

B. RECENT CARBON MONOXIDE EMISSION LEVELS

1. National Emission Levels

An estimated 137 x 10^9 kilograms (kg) (151 million tons*) of CO was emitted in the United States in 1969 (54 percent by weight of all major emissions for that year). In the Federal Republic of Germany, the total emissions of CO were estimated to be about 12.8 x 10^9 kg in 1970. Transportation sources accounted for about 8 x 10^9 kg from a motor vehicle population of nearly 8 million.

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*Units as measured in the United States are given in parentheses following the metric units.

Carbon monoxide emission estimates are derived by the use of emission factors and activity levels. Emission factors are developed from source-testing data, material balances, and theoretical calculations; activity levels are based on such quantities as vehicle distance of travel, fuel consumption, airplane landing and take-off cycles, and industrial process production.

In order to obtain detailed knowledge of the local and temporal distributions of all emissions from industries, domestic furnaces, and traffic, Dreyhaupt (5) proposed establishing an area-related emission register or inventory within the State of Nordrhein-Westfalen of the Federal Republic of Germany. The state government undertook a program to develop such an emission register in the industrial area of the city of Cologne in 1969. The details of establishing this register and the benefits to be derived are described in Reference (6).

2. Regional Emission Levels

Emission surveys have been conducted in various cities in the United States to determine the nature and amount of air pollutants emitted in those communities. Figure 3-1 presents the CO emissions from four different categories for 11 U. S. cities.

C. EMISSIONS AND EMISSION FACTORS BY SOURCE TYPE

1. Mobile Combustion Sources

a. Motor Vehicles

The largest single source of CO (almost 65 percent of the national total) in the United States in 1969 was the exhaust of motor vehicles, both gasoline- and diesel-powered. It should be pointed out that gasoline-powered motor vehicles contributed the largest amount (87 percent in 1969) of CO emissions from transportation sources.

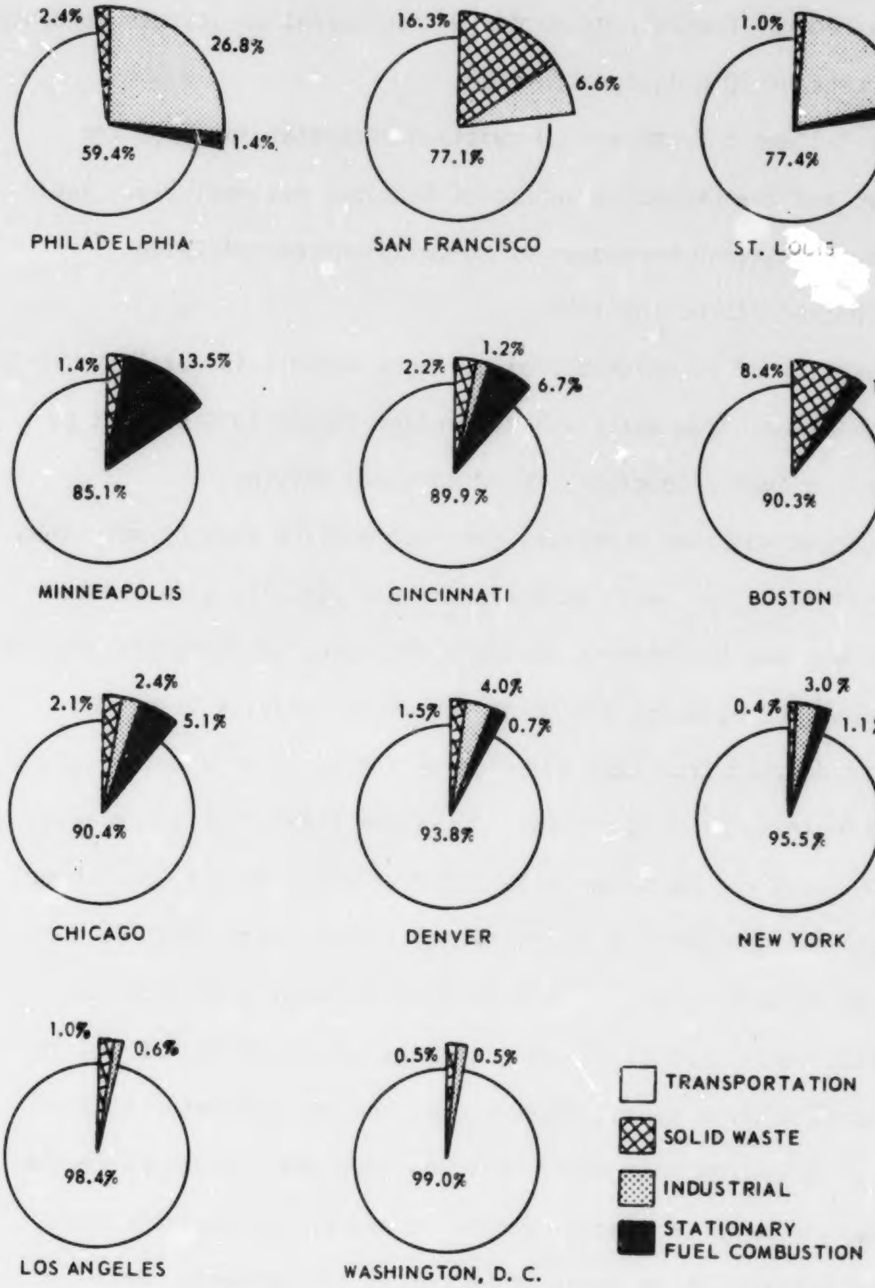

Figure 3-1. Carbon monoxide emissions by source category for various U.S.metropolitan areas in 1968.

In the Federal Republic of Germany, transportation sources accounted for about 62 percent of CO emissions in 1969.

Tables 3-1 and 3-2 present CO emission estimates for 1969 for the United States and the Federal Republic of Germany, respectively. Table 3-3 presents a more detailed breakdown of CO emissions and emission factors for the United States for 1969.

The quantity of CO emitted from a single vehicle is not large. The exhaust CO emissions from motor vehicles range from 1 to 4 percent by volume when averaged over a complete, representative driving cycle (7-12). Carbon monoxide emissions from automobiles vary by more than an order of magnitude. The lowest emitters are new vehicles with exhaust control systems, whereas the highest emitters are among uncontrolled vehicles.

The annual CO emission estimates for motor vehicles presented in Table 3-1 were derived from mass emission data from a large number of cars driven on simulated driving cycles. Emission rates for four classes of vehicles (one class for passenger cars and light-duty trucks, and three classes for heavy-duty trucks, including diesel trucks) were used. These emission rates were developed from vehicle activity data from the United States with consideration of vehicle operating characteristics, including urban-rural vehicle speed, vehicle age, and vehicle deterioration.

Exhaust emissions from motor vehicles have been expressed in the literature either in terms of concentrations in ppm of the contaminants emitted from the tailpipe or in terms of weight of contaminants per

Table 3-1. CARBON MONOXIDE EMISSION ESTIMATES BY SOURCE CATEGORY FOR THE UNITED STATES, 1969 (1)

Source	CO emissions, 10^9 kg/yr			Percent of total		
Transportation	101.0			73.7		
Motor vehicles		88.7			64.7	
Gasoline			87.8			64.0
Diesel			0.9			0.7
Aircraft		2.6			1.9	
Vessels		1.5			1.1	
Railroads		0.1			0.1	
Other non-highway use of motor fuels		8.2			5.9	
Fuel combustion in stationary sources	1.6			1.2		
Coal		0.7			0.4	
Fuel oil		0.1			0.1	
Natural gas		0.1			0.1	
Wood		0.9			0.6	
Industrial processes	10.8			7.9		
Solid waste disposal	7.2			5.2		
Miscellaneous	16.5			12.0		
Man made		7.9			5.8	
Forest fires		8.5			6.2	
Total	137.3			100.0		

Table 3-2. CARBON MONOXIDE EMISSION ESTIMATES BY SOURCE CATEGORY FOR THE FEDERAL REPUBLIC OF GERMANY, 1969

Source	CO emissions, 10^9 kg/yr	Percent of total
Transportation	8.0	62.5
Fuel combustion in stationary sources	3.0	25.4
Industrial processes	0.8	6.4
Miscellaneous	1.0	7.7
Total	12.8	100

distance traveled (e.g., g CO/km) (7-13). The latter method of expressing emissions is considered to be more representative and preferable because it is compatible with data for vehicle distance traveled in major metropolitan areas (13). Exhaust emissions expressed as ppm can be converted to weight per distance traveled if the exhaust volume per unit time and the vehicle speed (distance traveled) are known.

Adjustment of the basic emission data was made to account for differing average speeds in different areas. These speed conversion data, which are based on road tests of a number of vehicles under average traffic conditions, indicate that the average speed of a vehicle is a measure that provides an adequate index of emissions over a specific route pattern (9,13,14). This parameter, called average route speed, appears to reflect the engine power demand and consequent pollutant emissions that are associated with the acceleration, deceleration, cruise, and idle driving modes imposed by the many driving variables such as route, topography, traffic density, climate, and altitude.

Table 3-3. UNITED STATES CARBON MONOXIDE EMISSION ESTIMATES, 1969 (1)

Source	Emissions, 10^9 kg/yr	Emission factor[a]	
		Metric	U. S.
Mobile combustion sources			
Motor vehicles			
Light-duty vehicles-urban	48.3		
-rural	23.6		
Heavy-duty vehicles			
Class II (2700-4500 kg or 6000-10000 lb[b]) -urban	2.1		
-rural	1.6	Based on method described in text	
Class III (4500-8800 kg or 10000-19500 lb[b])-urban	1.8		
-rural	1.5		
Class IV (>8800 kg or >19500 lb[b]) -urban	3.9		
-rural	5.0		
Diesel	0.9		
Aircraft			
FAA control	1.0[c]	Based on LTO cycle - see text	
Military	1.2[c]		
Railroad	0.1	Distillate fuel oil: 8.4 kg/1000 liters	(70 lb CO/1000 gal)
Vessels	1.5	Distillate fuel oil: 8.4 kg/1000 liters	(70 lb CO/1000 gal)
Non-highway fuel uses	8.2	gasoline: 276 kg/1000 liters	(2300 lb CO/1000 gal)
Fuel combustion in stationary sources			
Coal			
Electrical power	0.2	500 g CO/1000 kg	(1.0 lb CO/ton)
Industrial	0.1[d]	750 g CO/1000 kg	(1.5 lb CO/ton)
Domestic and commercial	0.3	25 kg CO/1000 kg	(50.0 lb CO/ton)
Fuel oil			
Domestic, industrial, and miscellaneous	0.1	2.3 kg CO/100 kl	(8.4 lb CO/1000 bbl)
Electric power	N[e]	0.5 kg CO/100 kl	(1.7 lb CO/1000 bbl)
Natural gas			
Electric power	N	6.5 g CO/1000 m^3	(0.4 lb/10^6 ft^3)
Industrial	N	6.5 g CO/1000 m^3	(0.4 lb/10^6 ft^3)
Domestic and commercial	0.1	324 g CO/1000 m^3	(20 lb/10^6 ft^3)
Wood	0.9	22.5 kg CO/1000 kg	(45 lb CO/ton)
Industrial processes			
Foundries			
50% control	0.2	5 kg CO/1000 kg	(10 lb CO/ton of charge)
Uncontrolled	1.6	72.5 kg CO/1000 kg	(145 lb CO/ton of charge)
Petroleum refineries			
Fluid catalytic crackers	2.2	3.9 kg CO/100 liters	(13.7 lb CO/bbl of fresh feed
Fluid coking	0.1	8.6 kg CO/100 liters	(30 lb CO/bbl of fresh feed)
Moving-bed catalytic crackers	0.1	1.1 kg CO/100 liters	(3.8 lb CO/bbl of fresh feed)
Kraft pulp mills	0.9	35 kg CO/1000 kg	(70 lb CO/ton of product)
Carbon black			
Furnace	2.6	1750 kg CO/1000 kg	(3500 lb CO/ton of product)
Channel	1.0[f]		
Thermal	N		
Steel mills			
Beehive coke ovens	N	0.63 kg CO/1000 kg sinter	(1.27 lb/ton of sinter)
Basic oxygen furnaces	0.1	67.5 kg CO/1000 kg of sinter	(135 lb/ton of sinter)
Sintering	2.2	21 kg CO/1000 kg of sinter	(42 lb/ton of sinter)
Formaldehyde	0.1	50 kg CO/1000 kg of product	(100 lb CO/ton of product)
Solid waste combustion			
Incineration			
Municipal	0.3	17.5 kg CO/1000 kg	(35 lb CO/ton)
On-site	0.7	13.5 kg CO/1000 kg	(27 lb CO/ton)
Municipal open burning	3.1	42.5 kg CO/1000 kg	(85 lb CO/ton)
Metal conical burners	3.1	130 kg CO/1000 kg	(260 lb CO/ton-dry)
Miscellaneous combustion			
Building fires	0.2	30 kg CO/1000 kg	(60 lb CO/ton)
Forest fires	8.5	30 kg CO/1000 kg	(60 lb CO/ton)
Coal banks	0.3	25 kg CO/1000 kg	(50 lb CO/ton)
Agriculture	7.5	50 kg CO/1000 kg	(100 lb CO/ton)

[a] Some factors are weighted or estimated averages.
[b] Gross vehicle weight.
[c] Under 900 m (3,000 feet).
[d] Does not include 87.5 x 10^6 kg (96,400 U.S. tons) from coke plants.
[e] N = Negligible.
[f] Gross estimate.

Evaluation of auto exhaust data by Rose et al. (13) indicated that an empirical relationship between speed and CO emission level in pounds can best be satisfied or expressed by an inverse power function of the average route speed:

$$Y = AX^{-b}$$

where:
Y = weight of CO emitted
X = average route speed
A,b are constants.

$A = 970, \qquad b = -0.82$
based on the conditions in References (13,14).

The above equation does not apply when the engine is running but the car is standing still.

From this study and from the study of McMichael and Rose (14), it has been established statistically that average route speed is related more nearly to weight of emissions per unit of distance traveled rather than to exhaust concentration. When CO emissions from 40 randomly selected test vehicles in Cincinnati and Los Angeles were expressed in ppm and regressed on vehicle speed, the correlation coefficient was found to be 0.446 (0.31 to 0.58 at 95 percent confidence). For the same test, when CO emissions were expressed as pounds of CO per mile and regressed on vehicle speed (Figure 3-2), the correlation coefficient was found to be 0.613 (0.49 to 0.71 at 95 percent confidence). Further statistical analyses with individual vehicles showed that most of the observed variance could be attributed to differences among vehicles rather than to a poor correlation between CO weight emissions and route speed (Figure 3-3).

Carbon monoxide emissions are proportionately greater during the low-speed conditions below 32 kilometers per hour (20 mi/hr) because of an increase in frequency of the acceleration, deceleration, and

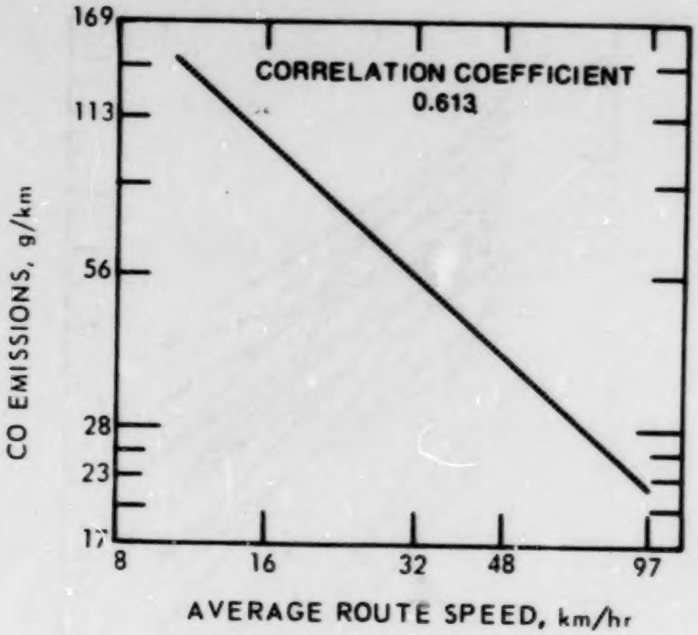

Figure 3-2. Effect of average route speed on carbon monoxide emission by weight (14).

idle stages of the driving cycle representative of heavier traffic (13). The same relationship between mass emissions and average route speed holds for the low air-to-fuel ratio operation encountered during high-altitude driving conditions (14).

It is important to note that the applicability of the curve in Figure 3-3 to controlled vehicles is questionable. It is reasonable to assume that carbon monoxide emissions from controlled vehicles prior to 1975 decrease somewhat with increasing average speed, but this relationship has not been accurately quantified to date. Because of the lack of data on the effects of control devices on 1975 and later vehicles, it would be premature to attempt to predict the relationship between emissions and average speed at this point in time.

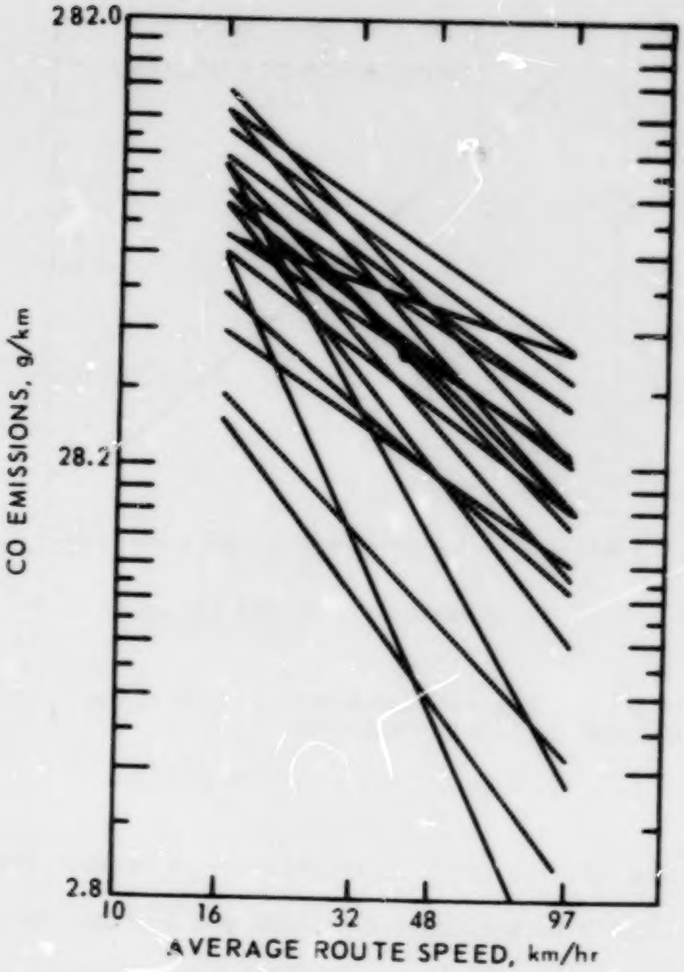

Figure 3-3. Carbon monoxide emissions by individual vehicles, Los Angeles (13).

The significance of the relationship between vehicle speed and CO emissions has not been fully exploited. The effects of the 1975 U. S. CO standard will not be fully realized until the mid-1980's in most metropolitan areas of the United States. In the interim, community and highway planners should recognize that high speeds of traffic within the urban area can effectively reduce the gross or overall CO emissions from the exhaust of pre-controlled 1975 automobiles.

The spark ignition engine produces considerably more CO than the diesel engine because of the former's different thermodynamic engine process. Under certain operating conditions such as idling, full power, etc., the spark ignition engine functions with fuel excess. With this knowledge it follows, from the principle of chemical thermodynamics, that CO must occur in the exhaust gas. The diesel engine, however, is driven in all operating ranges with air excess. Thus, the CO concentration in diesel exhaust gas is much lower in comparison to the CO in the exhaust gas from spark ignition engines.

In the investigations in the area of Cologne, as was done in Los Angeles (Figure 3-3), an average route speed was chosen for characterizing different driving conditions. From the results of the detailed investigations of driving conditions there, some different test cycles were evolved (15, 16). By means of these test cycles, vehicle emissions were determined on a chassis dynamometer. The test vehicles were chosen in such a way that the parameters that influence emissions (horsepower, age of vehicles, etc.) were simulated corresponding to the vehicle distribution in the Federal Republic of Germany. The first results obtained on 44 vehicles are shown in Figures 3-4, 3-5, and 3-6. Figure 3-4 shows the concentrations of CO, unburned hydrocarbons (HC), and nitrogen oxide (NO) in the engine exhaust gas, depending on the average driving speed (V_H). Figures 3-5 and 3-6 show the relationship between average emission factors of CO, unburned hydrocarbons, and nitrogen oxide in g/hr and g/km and vehicle speed.

b. Aircraft

The contribution from aircraft to the total atmospheric CO pollution burden in the United States is approximately 3 percent. A

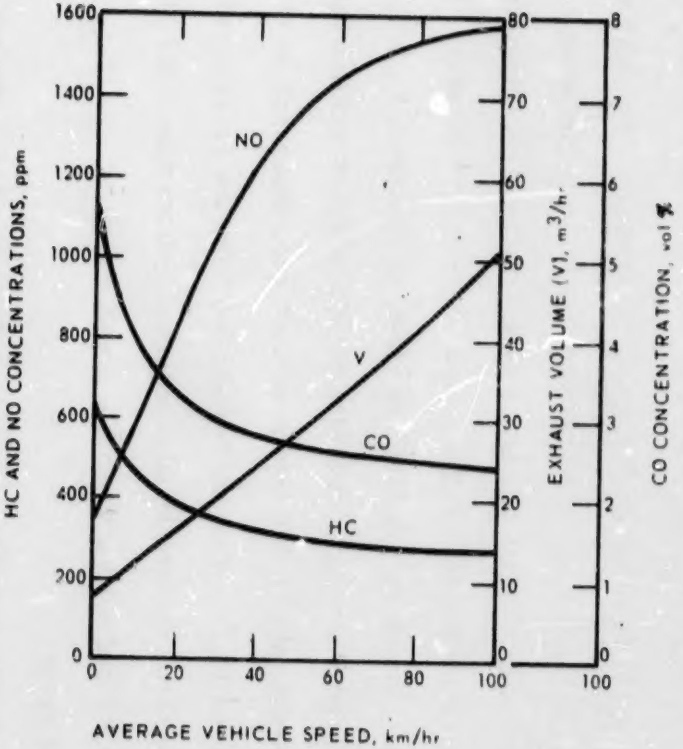

Figure 3-4. Relationship between average vehicle speed and carbon monoxide, hydrocarbon, and nitrogen oxide concentrations in auto exhaust.

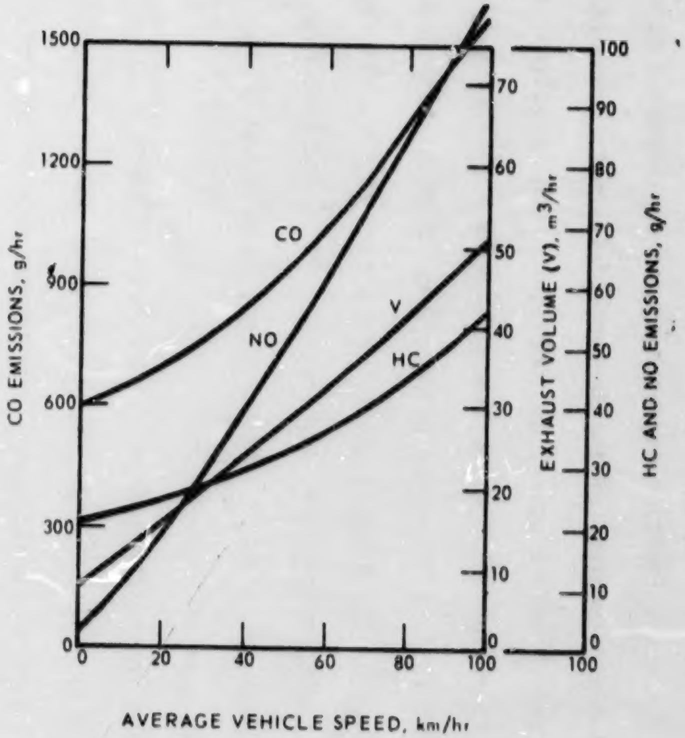

Figure 3-5. Relationship between average vehicle speed and carbon monoxide, hydrocarbon, and nitrogen oxide emission factors (g/hr).

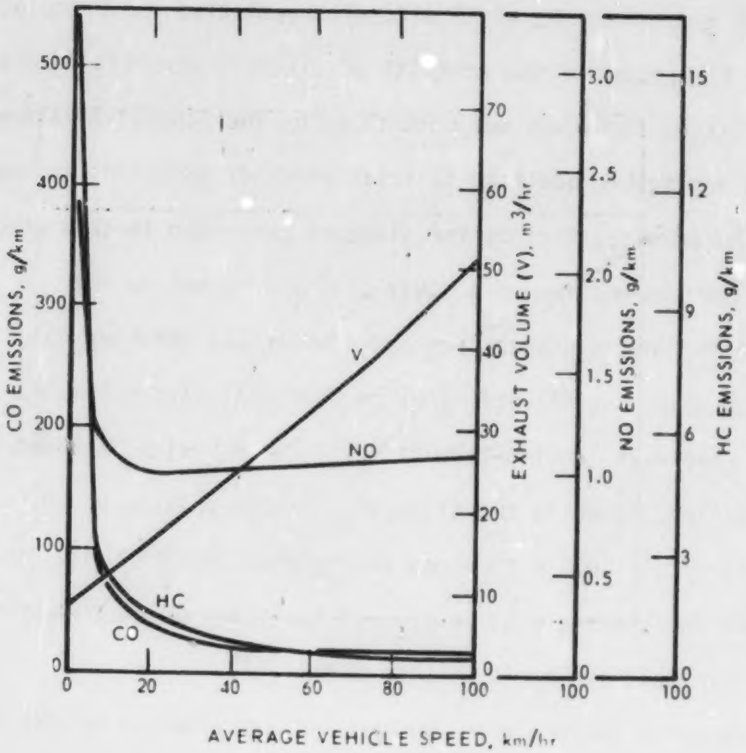

Figure 3-6, Relationship between average vehicle speed and carbon monoxide, hydrocarbon, and nitrogen oxide emission factors (g/km).

projection of the potential rise in total CO emissions from the civil aircraft population between 1967 and 1979 has been estimated to be 59 percent over the base figure of 0.84×10^9 kg (0.93 million tons) calculated for 1967 (17). Although the contribution of aircraft to total CO emissions is small at this time, atmospheric concentrations of CO at and near airports may be creating a localized problem.

The civil aircraft population is the source of approximately half of the CO emissions attributed to aircraft; military aircraft contribute the remaining half. Civil aircraft may be classified as: private aircraft (> 99 percent piston powered) and commercial carriers (> 85 percent turbine powered). Commercial carriers, while constituting only about 2 percent of the civil aircraft population, nevertheless account for 20 percent of the activity at civilian aircraft terminals. Civil aircraft at terminals not controlled by the Federal Aviation Administration represent a negligible addition to total aircraft emissions in the United States.

The emission factors for aircraft presented in this chapter, estimated from the results of a study (17) and report to the Congress of the United States, are based on actual sampling data.

Emissions at elevations below 3000 feet were estimated on the basis of a five-mode landing-takeoff (LTO) cycle, which included approach, landing, taxiing, takeoff, and climbout. Though only about 20 percent of the total aircraft fuel is consumed during the LTO cycle, the cycle accounts for approximately 83 percent of the total CO emitted during an entire trip (LTO cycle plus cruise mode) (17).

Emission factors were derived and expressed as weight of CO emitted per unit time by a particular class of aircraft operating in a particular mode. Knowledge of the time-frequency distribution by class and mode allowed calculation of the total aircraft CO emissions presented in Tables 3-1 and 3-3.

A comprehensive survey of the research on emissions from aircraft engines is given in Reference (18). A paper on aircraft emissions is being prepared by the Advisory Group for Aerospace Research and Development (NATO), and an expanded and updated report on aircraft emissions (19) has recently been published by the U. S. Environmental Protection Agency (U.S.EPA).

c. Other Non-Highway Mobile Sources

According to U. S. Bureau of Mines data and a study currently being conducted for the U. S. EPA, the total non-highway use of motor fuels, excluding aircraft, amounted to 31 billion liters (8.20 billion gallons in 1969 for the United States (20-22). This total represents the consumption of gasoline and diesel fuel by trains, ships, agricultural machinery, commercial equipment, and construction machinery. Trains and ships also consumed distillate fuel oil, residual fuel oil, and coal.

The emissions of CO were calculated with emission factors of 276 kg CO/1000 liters of gasoline (2300 pounds CO/1000 gallons) and 8.4 kg CO/1000 liters of the other liquid fuels (70 pounds CO/1000 gallons). The emission estimates are presented in Tables 3-1 and 3-3.

2. Carbon Monoxide from Combustion for Power and Heat

The combustion of coal, fuel oil, natural gas, and wood to produce power and heat also produces a small, but significant, quantity of CO on a national scale in the United States. On a smaller scale, other fuels such as bottled gas and kerosene are used for miscellaneous heating purposes. By far the largest percentage of CO emissions in each fuel category may be attributed to residential, commercial, institutional, and light industrial burning. This large portion is caused by the relatively inefficient nature of combustion associated with these facilities.

The following categories were included in the estimation of the quantity of CO from coal, gas, and oil combustion presented in Table 3-1: electric power utilities, coke plants, steel and rolling mills, cement mills, oil refineries, other manufacturing and mining industries, military, residential, commercial, institutional, and light industrial.

Coal and wood combustion account for the majority of CO emissions in the stationary combustion source category. Approximately 460 billion kg

(507 million tons) of lignite and bituminous coal and 7.9 billion kg (8.8 million tons) of anthracite coal (excluding trains and ships) were consumed in the United States in 1969 (21). Electric power utilities and industries are the largest consumers of coal, but account for only about 28 percent of the emissions from this fuel. Total wood consumption by user category is not available. Total energy from wood combustion, however, was estimated to be 745 x 10^{12} Btu for 1969. Assuming 9000 Btu per pound of wood, the nearly 42 x 10^7 tons of wood consumed resulted in emissions of approximately 900 million kg (1 million tons) of CO, as indicated in Table 3-1. Approximately 104 billion kg of coal and lignite (black and brown coal) was consumed in the Federal Republic of Germany in 1970.

Approximately 97 x 10^9 liters (607 million barrels) of distillate fuel oil and 101 x 10^9 liters (634 million barrels) of residual fuel oil were consumed in stationary fuel combustion sources in 1969 in the United States (20). Nearly 60 percent of the total fuel oil was consumed for space-heating purposes in residential, commercial, institutional, and light industrial sources. In the Federal Republic of Germany in 1970, approximately 82 x 10^9 liters (516 million barrels) of distillate fuel oil was consumed in stationary fuel combustion sources.

Total gas consumption, of which 99 percent consists of natural gas, exceeded 616 x 10^9 m^3 (22 trillion ft^3) in 1969 (23). Electrical power utilities consumed about 16 percent of the total, and residential, commercial, institutional, military, and industrial sources accounted for the remainder.

3. Industrial Processes Producing Carbon Monoxide

Industrial processes emit varying quantities of CO into the atmosphere. The five largest sources of this pollutant are petroleum refineries, iron foundries, kraft pulp mills, lamp black plants, and sintering plants. Other sources for which emission estimates were made are steel mills and formaldehyde manufacturers. Emission factors for these processes are based on analysis of sampling data; however, the lack of published data from other sources on production, types of equipment, and controls, as well as emission factors, makes it impossible to include estimates of emissions for them. Some other sources of CO include ammonia and methanol reforming, synthesis gas manufacture, organic chemical manufacture (acids, esters, ketones, and aldehydes), reactive metals manufacture, and nonferrous secondary smelting.

The major source of CO in iron foundries is the cupola. In 1969, 22 billion kg (24.4 million tons) of iron was charged to cupolas in the United States, with approximately 10 to 20 percent of this production subject to 90 percent afterburner control. In the Federal Republic of Germany, about 900 cupolas with a total production of 4 billion kg (4.4 million tons) of pure iron were operating in 1970. In the absence of an afterburner, hot-air cupolas have an emission factor of 0.16 kg CO/kg of charge.

The major sources of CO in petroleum refining operations in the United States are the catalytic cracking units. The emissions of CO from roughly 75 percent of these units are nearly 100 percent controlled by waste-heat boilers.

The major sources of CO in kraft paper mills are the lime kilns and the kraft recovery furnaces. These sources produced 25 billion kg (27.6 million tons) of pulp in 1969 and emitted CO that was not subject to control.

The sintering of blast furnace feed is another major source of CO; 1969 production of both sinter and pellets is estimated to have totaled 98 billion kg (108 million tons).

The emissions from these major industrial sources were calculated as shown in Table 3-3.

4. Solid-Waste Combustion

The total annual solid-waste production in the United States has been estimated to be about 334 billion kg (368 million tons). About half of this solid waste is disposed of through incineration and open burning. This combustion results in the production of 7.3 billion kg (8 million tons of CO). In the Federal Republic of Germany, annual solid-waste production in 1969 amounted to 43 billion kg (47 million tons).

An estimate of the per-capita solid-waste generation rate was obtained from the results of a study by the U. S. National Center for Urban and Industrial Health on collected solid wastes (24), and from estimates by the National Air Pollution Control Administration on uncollected solid wastes. This estimate (4.5 kg/day or 10 lb/day per person), population figures, and information on the proportions of the various solid-waste disposal methods allowed estimation of the national CO emissions from this category.

5. Miscellaneous Combustion

The miscellaneous combustion category includes emission estimates from both uncontrolled and controlled forest fires, agricultural waste burning, structural fires, and coal-refuse-bank fires. These totals, however, do not include the burning of forest and crop residues.

The United States Forest Service estimates that over 2,304,450 hectares (5,690,000 acres) of forest was destroyed by wild (unprescribed) fires during 1969 (25). In addition, over 243,000 hectares (600,000 acres) of controlled (prescribed) burning occurred in national parks. Prescribed burning by industry and private interests accounted for 1,183,000 hectares

(2,920,000 acres). An average of 90,000 kg of wood/hectare (40 tons/acre) was burned in wild fires, and 49,000 kg/hectare (22 tons/acre), was burned in controlled fires. The total emission estimates presented in Tables 3-1 and 3-3 were calculated by applying an emission factor of 50 kg CO/1000 kg (100 pounds CO/ton), of burned material for agricultural open burning. In addition, 204 billion kg (225 million tons) of agricultural waste is generated each year (24). It is estimated that half of this agricultural waste is burned in the open. Using an estimated emission factor of 30 kg CO/1000 kg (60 pounds CO/ton) for open burning, the estimate for this source was calculated.

The National Fire Protection Association (U.S.) reports that nearly a million buildings were attacked by fire in 1969 with a 20 to 30 percent extent of destruction. The estimates of CO emissions from structural fires were based on these assumptions and an average emission factor for wood burning of 30 kg CO/1000 kg (60 pounds CO/ton).

The U. S. Bureau of Mines estimates that 150 million m^3 (5.4 billion ft^3) of burning coal refuse piles existed in the United States in 1969, that the density of these coal piles averages 1600 kg/m^3 (100 $pounds/ft^3$), and that, on the average, one of these coal banks will burn for 20 years (26). With these assumptions, the emissions from this source were estimated by using an emission factor for coal combustion of 25 kg CO/1000 kg (50 pounds CO/ton) of coal burned.

D. PROJECTIONS OF CARBON MONOXIDE EMISSION LEVELS

Two factors must be considered in projecting future CO emission levels. The first factor is the potential increases caused by population growth--more motor vehicles and aircraft, expansion of industry, and the increased use of fuel combustion for power and heat to be expected in the coming decades. The second, and opposing, factor is the application of more effective control technology. For the major CO emitter in the United States, motor vehicles, no further increase in the magnitude of CO emissions would be expected before the year 2000 because of present and anticipated CO control measures required by existing Federal Statutes.

Because of a lack of published data, no projections have been made for CO emissions from stationary sources. The national magnitude of CO emissions from these sources is expected to increase, although it is recognized that changes in fuels, industrial processes, and methods of solid waste disposal may result in decreases in CO emissions from specific sources.

In the Federal Republic of Germany and other European countries (5), the CO (and HC) emissions are limited by law (since 1971) for new vehicles. Because of the increase in motor vehicles and the low rate of decrease in the number of old vehicles that have no limitation of CO, reduction of CO emissions can be expected to occur only after 1975. Because of increasing electrification, the CO emissions of railroad traffic have decreased. Regarding aircraft, an increase in CO emissions, attributable to an increase in air traffic, can be expected. The CO emissions of industry, especially power plants, will be influenced by atomic energy reactors; thus an overall decrease of CO emissions in the future can be expected. A decrease in CO emissions from domestic furnaces can be expected because the use of gas and electricity for heating is increasing.

E. SUMMARY

Annual carbon monoxide emissions from major sources in the United States were estimated to be 137 x 10^9 kg (151 million tons) for the year 1969. In the Federal Republic of Germany, annual CO emissions for 1969 were estimated to be 12.8 x 10^9 kg (14 million tons). In the United States, the largest single source was the gasoline-powered motor vehicle, which accounted for 88 x 10^9 kg (99 million tons), or over 64 percent of the total. Internal combustion engines used in aircraft, non-highway use, trains, ships, and diesel-powered motor vehicles accounted for another 10 percent of the total. Other major sources included fuel combustion in stationary sources, industrial processes, solid-waste combustion, and forest fires.

Although carbon monoxide emission totals were found to differ among different regions of the United States, the highest estimates ranged up to about 5 x 10^9 kg (5 million tons) per year in New York and Los Angeles. In all but 2 of 26 cities surveyed, the CO emissions were the largest component of the total tonnage of pollutants emitted to the atmosphere. The major source of CO emissions in all of the regions studied was the motor vehicle.

Generally, it can be said that in the concentrated-traffic areas, the CO emissions from motor cars will predominate. In order to get detailed information, however, it will be necessary to make intensive investigations regarding the local and temporal distribution of CO emissions from all emitters--traffic, industries, domestic furnaces, etc.

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CHAPTER 4.

MEASUREMENT OF CARBON MONOXIDE CONCENTRATIONS IN AMBIENT AIR

A. INTRODUCTION

Because of the need to measure the wide range of CO concentrations found in community air (from less than 1 to about 450 mg/m^3), numerous measurement techniques have been developed. Standardization of CO in air samples for measurements and subsequent measurement by available aerometric techniques are discussed in this chapter. Gas samples may be standardized by volumetric, gravimetric, and chemical techniques. The methods available for continuous measurement of CO include: nondispersive infrared (NDIR) analysis, electrochemical analysis, mercury vapor analysis, gas chromatography, and catalytic and electrolytic analysis. The methods available for spot or integrated measurements include: nondispersive infrared analysis, infrared spectrophotometric analysis, gas chromatographic analysis, and colorimetric analysis.

In the United States, several tentative methods for the determination of CO in ambient air have been prepared for collaborative testing and evaluation as possible standards by the Intersociety Committee on Manual of Methods of Air Sampling and Analysis. Hopefully, one or more of these methods will qualify as a standard method against which all instruments and methods may be calibrated (1). The U. S. Environmental Protection Agency has adopted nondispersive infrared spectrometry as its reference method in determining compliance with national air quality standards for CO (2,3). The Commission on Air Hygiene of the German Society of Engineers has accepted nondispersive infrared analysis as a standard method of measuring CO concentrations in ambient air (4).

A number of variables require consideration when atmospheric CO is to be measured (5). They include: the sampling method, the choice of sampling area (6,7), the specific location within an area and the exact height above the ground (8), the influence of meteorological conditions (9), and the influence of vehicular emissions (10) and other local pollutant sources.

B. PREPARATION OF CARBON MONOXIDE GAS STANDARDS

1. Volumetric Gas Dilution Techniques

Accurately prepared CO gas standards must be available for the calibration of methods and measuring instruments before CO levels can be quantified. Volumetric gas dilution is the technique used most frequently for the preparation of standards. If a large quantity of standard gas is needed, the dilution may be made in pressurized tanks (11,12). Care should be exercised to assure accuracy of the standard because CO in pressurized tanks may be unstable at concentrations of less than 1 mg/m^3 (1 ppm).

It is important in these operations to verify that the diluting gas is free of CO. Some investigators suggest that pure helium, which is reliably free of CO, is preferable to nitrogen as a diluent. A less expensive method is to use helium periodically as a true "zero" gas to estimate the CO content in the nitrogen diluent. A correction factor is then used to account for the CO content in the nitrogen.

2. Gravimetric Methods for Standardizing Carbon Monoxide Gas Mixtures

Gravimetric methods are not used routinely in air pollution studies to measure CO because relatively large samples are needed to quantify

CO concentrations. These methods are useful, however, for checking CO standards. McCullough et al. (13) made use of the reaction:

$$\text{CO (gas)} + \text{HgO (solid, red)} \xrightarrow{(175^\circ \text{ to } 200^\circ\text{C})} \text{Hg (gas)} + \text{CO}_2 \text{ (gas)}.$$

During the passage of the gas sample, the red mercuric oxide is reduced and loses weight. This weight loss value and the measured volume of the sample are used to calculate the concentration of CO present in the standard gas mixture.

Salsbury et al. (14) used a method in which the gas containing CO is drawn over Hopcalite at 195 °C and the carbon dioxide formed is absorbed in tubes containing Ascarite (NaOH-asbestos). Gas volumes are determined using a flowmeter and a stopwatch. From the weight of the CO_2 absorbed in the tubes, the CO concentration is calculated. This method is accurate to about 2 percent for CO concentrations of from 25 to 1000 mg/m^3 (22 to 870 ppm).

Lysyj et al. (15) oxidized CO to CO_2 with decomposed silver permanganate ($AgMnO_4$) as a catalyst and weighed the CO_2 absorbed in an Ascarite tube.

3. Chemical Assay of Carbon Monoxide Gas Standards

The reduction of iodine pentoxide may be used to measure CO in standard gas mixtures. Adams and Simmons (16) have given a detailed discussion of the method. The analysis is based on the reaction:

$$5CO + I_2O_5 \longrightarrow 5CO_2 + I_2.$$

When the gas mixture containing CO is passed over heated I_2O_5, iodine is liberated. It is then collected and titrated with standard sodium thiosulfate.

C. MEASURING CARBON MONOXIDE IN ATMOSPHERE

1. Continuous Measurement of Carbon Monoxide

a. Definitions of Terms Describing Instrument Performance

Definitions of some terms commonly used to describe instrument performance are given below; in this document these terms will be used as defined throughout this chapter.

Sensitivity. The sensitivity of a measuring device is the ratio of the observed change indicated by the device to the change of the variable that caused the change of indication.

Minimum detectable concentration. The minimum detectable concentration is the 99.9th percentile of the indicated concentrations when the input is zero, or expressed as 3 σ of the background. The limit of certainty is two times the minimum detectable concentration.

Response time. The amount of time taken by an instrument from the start of a change in input until the instrument output reaches a specified percentage of the ultimate change. (The specified percentage is usually 90 or 95.) The response time is a measure of the minimum averaging time necessary to achieve valid output data.

Lag time. The time between the start of an input signal and the observed start of the output response corresponding to that signal. The lag time is a measure of the delay between input sample and output data and is always less than or equal to the response time.

Accuracy. The degree of agreement of the true value with the indicated value or values.

True value. The number that is completely consistent with the (known) value and definition of the primary standard used.

Reproducibility. The reproducibility for independent measurements is defined as the 3 σ -range of the measured values, under the condition that the measured values of a definite quantity are randomly distributed.

b. Nondispersive Infrared Analyzers

Nondispersive infrared (NDIR) analyzers are the most commonly used continuous, automated devices for determining atmospheric CO and are generally accepted as being the most reliable reference device for the calibration of other instruments. An NDIR analyzer operates on the principle (17) that CO has a sufficiently characteristic infrared absorption spectrum and that the absorption of infrared radiation by the CO molecule can be used as a measure of CO concentration in the presence of other gases (18). Although the size, shape, sensitivity, and range of these instruments vary with the manufacturer, basic components and configurations are similar. Most commercially available instruments include a hot filament source of infrared radiation, a rotating sector (chopper), a sample cell, a reference cell, and a detector. The detector senses pressure changes on either side of a diaphragm separating portions of gases being irradiated through the sample cell or the reference cell of the instrument. These pressure changes are converted to electrical signals corresponding to the difference between radiation received from the sample and the reference cells. The signal is amplified and rectified, and then read on a meter or recorder calibrated to yield CO concentration.

Most commercially available instruments function on the double-beam principle, operate at atmospheric pressure, and detect minimum CO concentrations of about 0.6 to 1.2 mg/m^3 (0.5 to 1.0 ppm). The sensitivity of NDIR instruments and the minimum concentrations that they can detect are proportional to the length of the cells, the electronic amplification, and the operating pressures. Measuring ranges usually extend from 1 to 58 mg/m^3 (1 to 50 ppm) CO or from 1 to 115 mg/m^3 (1 to 100 ppm) CO. Newer NDIR instruments, however, may be used to measure from 1 to 29 mg/m^3 (1 to 25 ppm) CO at atmospheric pressure and with cell path lengths of less than 0.5 meter.

NDIR analyzer response times are determined by the physical dimensions of the system, the flow rate of the sample, and the response time of the meter or recorder. Response times may range from less than 1 to 5 minutes.

Carbon dioxide and water vapor interfere in the determination of CO by NDIR techniques. Filter cells used to minimize these interferences may be placed in front of the sample cell or in front of both sample and reference cells. Filter cells filled with carbon dioxide and water vapor absorb radiation at interfering wavelengths so that normal atmospheric concentrations of CO_2 and water vapor in the sample have minimal effect on the radiation reaching the detector (19).

Optical filters are also used to limit the infrared wavelength and bandwidth to a range in which CO_2 and water vapor are transparent and thus invisible to the instrument.

Other techniques may be used to minimize or prevent CO_2 interference. Tubes filled with CO_2 absorbant remove CO_2 from the entering gas stream; other systems add nominal quantities of CO_2 (300 to 400 ppm) to the zero and span gases used to calibrate the NDIR instrument.

Filter cells reduce water vapor interference; however, they do not adequately cope with the high absolute humidities that are frequently encountered in atmospheric monitoring. Figure 4-1 shows the effect of water vapor on a typical NDIR analyzer uncompensated for water vapor interference (20). Air streams may be dried by using dehydrating agents such as silica gel, anhydrous calcium sulfate, magnesium perchlorate, or combinations of these media (21,22). Jacobs et al. (23) found anhydrous calcium sulfate to be unsatisfactory for the removal of water vapor from the gas stream. Satisfactory results were obtained by saturating the incoming air with water at a constant temperature, thus eliminating

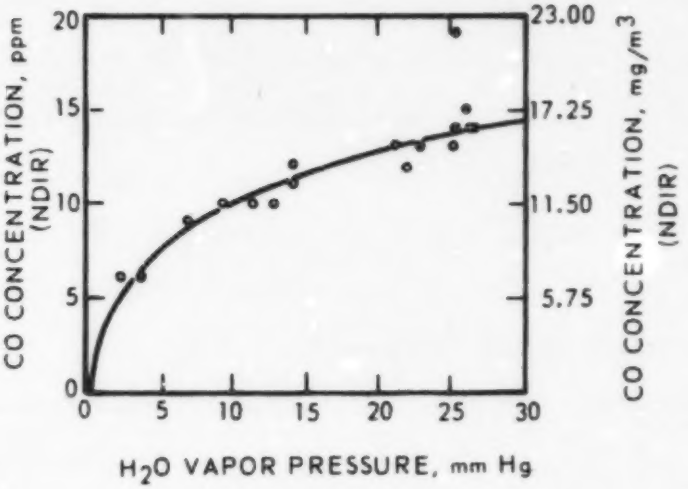

Figure 4-1. Typical nondispersive infrared analyzer response to water vapor (20).

water as a variable. Some commercially available instrument systems use this technique to eliminate water vapor interference. Others reduce water vapor interference by passing the air sample through a refrigerator in front of the analytical system to condense moisture from the air. This system, however, cannot regulate the absolute humidity in the air stream undergoing analysis when the dew point of the sample air is lower than the refrigerator temperature (as is the case in cold weather or with pressurized calibration gases). It should be realized that most methods of reducing CO_2 and water vapor interferences also tend to reduce instrument sensitivity or increase instrument response time, or both.

A new type of NDIR analyzer-detector has been developed (24). Both cells of the radiation receiver are in series instead of in parallel. The radiation after passing through the reference and the sample cell is received by the same detector cell. Using this technique, water vapor and CO_2 interferences may be disregarded.

NDIR systems have several advantages. They are not sensitive to flow rate, they require no wet chemicals, they are reasonably independent of ambient air temperature changes, they are sensitive over wide concentration ranges, and they have short response times. Further, NDIR systems may be operated by nontechnical personnel. Such systems also have some disadvantages such as zero drift, span drift, nonlinearity, and high cost. Some newer instruments have minimum drift because good quality thermostats and solid state electronics are used in their manufacture. Such instruments also have automatic zeroing, spanning, and recalibrating capability; they may also be obtained with essentially linear outputs. Features such as these should be considered when multiple-station networks are established.

c. Electrochemical Analyzers

1) Galvanic analyzer. Galvanic cells employed in the manner described by Hersch (25,26) can be used to measure atmospheric CO continuously. When an air stream containing CO is passed into a chamber packed with I_2O_5 and is heated to 150 °C, the following reaction takes place:

$$5CO + I_2O_5 \xrightarrow{(150\ °C)} 5CO_2 + I_2.$$

The liberated iodine is absorbed by an electrolyte and transferred to the cathode of a galvanic cell. At the cathode, the iodine is reduced, and the resulting current is measured by a galvanometer. Instruments using this detection system have been used successfully to measure CO levels in traffic along freeways (27).

Mercaptans, hydrogen sulfide, hydrogen, olefins, acetylenes, and water vapor interfere. Water may be removed by sampling through a drying column; hydrogen, hydrogen sulfide, acetylene, and olefin interferences can be minimized by sampling through an absorption tube containing mercuric sulfate ($HgSO_4$) on silica gel.

2) Coulometric analyzer. A coulometric method employing a modified Hersch-type cell has been used to measure CO in ambient air on a continuous basis (22). The iodine pentoxide (I_2O_5) reaction with CO liberates iodine. The iodine is then passed into a Ditte cell, and the current generated is measured by an electrometer-recorder combination. Interferences are the same as those discussed above for the galvanic analyzer (28,29).

This technique may be used for a minimum detectable concentration of 1 mg/m^3 (1 ppm) with good reproducibility and accuracy if flow rates and temperatures are well controlled. This method requires careful column preparation and use of filters to remove interferences. Its relatively slow response time may be a disadvantage in some work.

d. Mercury Vapor Analyzer

A continuous CO analyzer using the reaction of CO with hot mercuric oxide and photometric determination of the mercury vapor produced has been developed and used (17). The reaction involved is:

$$CO + HgO(s) \xrightarrow{(210\ °C)} CO_2 + Hg(g).$$

Oxygenated hydrocarbons and olefins react quantitatively and, therefore, present a major interference; however, these are normally present in the ambient atmosphere in low concentrations relative to CO. Free hydrogen also interferes with the technique, but this interference is not serious because very little free hydrogen is present in the air. The effect of ozone has not been reported, but ozone, too, is normally present in the atmosphere in very low concentrations relative to CO.

The mercury vapor instrument has a response time similar to that of the NDIR analyzer; but because of interferences and some electronic instability, it does not appear to be suitable for routine urban atmospheric monitoring. The instrument is, however, a useful, portable, continuous analyzer with a capability for analyzing concentrations of from 0.029 to 11.5 mg/m^3 (0.025 to 10.0 ppm) of CO. Changes of 0.002 mg/m^3 (0.002 ppm) are detectable. For this reason it has found application in determining geophysical "background" CO levels throughout the world. An instrument operating on the same principle was developed by Seiler (30). This instrument has no interferences from hydrocarbons, olefins, hydrogen, or ozone. The detection limit is about 0.0001 mg/m^3 (1 ppb) of CO. This instrument has performed continuously over a period of at least 3 months with only routine maintenance. Calibration is automatic and baseline is internally compensated. The standard deviation is ± 3 percent at a mixing ratio of 0.1 ppm.

e. Gas Chromatographic Analyzer

A prototype automated gas chromatographic system has been developed to measure both CO and methane (31). A gas sampling valve, back flush valve, precolumn, molecular sieve column, catalytic reactor, and flame ionization detector comprise the system. The precolumn prevents CO_2, water, and hydrocarbons other than methane from reaching the molecular sieve. The catalytic reactor quantitatively converts CO to methane, which is then measured by the flame ionization detector. The system is designed for semicontinuous operation with the capability of performing one analysis about every 5 minutes. It has a linear output for both CO and methane, and has a wide operating range suggesting its use in both heavily polluted areas and relatively clean locations. Simultaneous CO and methane concentrations of from 0.1 to 1150 mg/m^3 (0.1 to 1000 ppm) can be measured with this instrument. Its semicontinuous characteristics suggest its use in special surveys and field studies rather than for routine air monitoring. The fact that the instrument must be operated by technically trained personnel can be considered a possible disadvantage.

f. Catalytic Analysis

Carbon monoxide may be oxidized catalytically to CO_2 using Hopcalite; the resulting temperature rise is recorded continuously and is used to indicate CO concentrations (32,33). Although these systems are widely used in enclosed spaces, their applicability for routine ambient air monitoring is limited because they function best at high ambient concentrations.

2. Intermittent Analysis

a. Collection of Spot or Integrated Samples

Intermittent samples may be collected in the field and later analyzed in the laboratory. A detailed outline of this technique has been given by Chovin et al. (34, 35), and Mueller (36).

Sample containers may be rigid (glass cylinders or stainless steel tanks) or nonrigid (plastic bags). Because of cost and other considerations, intermittent sampling may be the only practical method for air monitoring using these techniques. Samples can be taken over a few minutes or accumulated intermittently to obtain, after analysis, either "spot" or "integrated" results. Techniques for analyzing intermittent samples are described below (5).

b. Nondispersive Infrared Analysis

Field NDIR continuous monitoring analyzers discussed previously can also be used for laboratory analysis of intermittent samples. NDIR instruments are designed by some manufacturers primarily for use in the laboratory and must be modified for continuous ambient air monitoring in the field.

c. Infrared Spectrophotometric Analysis

Carbon monoxide may be measured by its infrared absorption at a wavelength of 4.6 micrometers (μm). Other gases may absorb at this wavelength, but they can be differentiated from CO by examining the complete spectrum from 2 to 15 μm. The sensitivity and range of the technique depend on the sophistication of the instrument used. A minimum detectable concentration of 2.9 mg/m^3 (2.5 ppm) CO has been obtained by instruments using scale expansion and a 1-meter path-length cell (37). It can be expected that a similar infrared spectrophotometer equipped with a 10-meter cell and ordinate scale expansion would have a 0.3 mg/m^3 (0.3 ppm) CO detection capability. Water vapor and CO_2 must be removed from the sample before the infrared scan can be made; in most applications magnesium perchlorate and Ascarite are used to remove interfering substances. The technique is specific and accurate, but requires expensive, nonportable equipment.

d. Gas Chromatographic Analysis

After reduction of CO over a reduced nickel catalyst, the gas chromatograph equipped with the flame ionization detector discussed earlier becomes a satisfactory tool for determining low levels of CO (20,31,38-40). One mole of CO produces 1 mole of methane. Since methane may be detected at concentrations of about 0.01 ppm, it is possible to detect that concentration of CO (41). The technique does not suffer from interferences because the measurement is made on a methane peak derived from a separated CO peak. Operating temperatures and other parameters must be controlled, however, before reliable results can be obtained.

e. Colorimetric Analysis

1) Colored silver sol method. Carbon monoxide reacts in an alkaline solution with the silver salt of p-sulfamoylbenzoate to form a colored silver sol. Concentrations of from 12 to 23,000 mg/m^3 (10 to 20,000 ppm) CO may be measured by this method (42-46). The procedure has been modified to determine CO concentrations in incinerator

effluents (28). Samples are collected in an evacuated flask containing the silver sol. The absorbance of the resulting colloidal solution is measured spectrophotometrically. Acetylene and formaldehyde interfere, but can be removed by passing the sample through mercuric sulfate impregnated on silica gel. Carbon monoxide concentrations of 6 to 20,700 mg/m^3 (5 to 18,000 ppm) may be measured with an accuracy of 90 to 100 percent.

2) U. S. National Bureau of Standards colorimetric indicating gel. A National Bureau of Standards (NBS) colorimetric indicating gel (incorporating palladium and molybdenum salts) has been devised to measure CO in the laboratory and in the field (47,48). The laboratory method involves colorimetric comparison of samples with freshly prepared indicating gels exposed to known concentrations of CO. The method has an accuracy range of 5 to 10 percent of the amount of CO involved, and the minimum detectable concentration is 0.1 mg/m^3 (0.1 ppm). This technique requires relatively simple, inexpensive equipment, but oxidizing and reducing gases interfere, and the preparation of the indicator tube is a tedious and time-consuming task.

3) Length-of-stain indicator tube. An indicator tube method using iodineperoxide (49,50) and potassium palladosulfite (51) is a commonly used method. Carbon monoxide reacts with the contents of the tube and produces a green color or a discoloration. The length of the color or the discoloration is an exponential function of the CO concentration. This method and other indicator tube methods are

estimated to be accurate to within ± 25 percent of the amount present, particularly at CO concentrations above approximately 24 mg/m^3 (20 ppm).

Such indicator tube methods have been used frequently in air pollution studies. Ramsey (52) used the technique to measure CO at traffic intersections, and Brice and Roesler (53) used color-shade detector tubes to estimate CO concentrations with an accuracy of ± 15 percent.

Colorimetric techniques and length-of-stain discoloration methods are recommended for use only when the other physicochemical monitoring systems are not available. They may be used in the field where accuracy is not required and can be of great qualitative value during air pollution emergencies.

D. SUMMARY

Because CO levels exist over such a wide concentration range, the use of a wide variety of chemical and physical procedures may be required to adequately evaluate atmospheric concentrations. The accuracy of any method used can be no better than the standards used to calibrate the instrument or method used. When pure CO and CO-free nitrogen are available, volumetric gas dilution techniques are satisfactory ways to prepare standard gases. Gas mixtures of doubtful or unknown concentrations of CO may be assayed by the gravimetric and chemical (iodine pentoxide) standardization methods. These procedures are time-consuming, but accurate.

The continuous measurement of atmospheric CO can be accomplished by using a variety of techniques. The most commonly used device is the nondispersive infrared (NDIR) analyzer, which is sensitive, but subject to a number of interferences. These interferences, however, may be removed or minimized by proper treatment of the air stream.

New NDIR analyzers can measure CO in the range of from 1 to 29 mg/m^3 (1 to 25 ppm), and can be equipped with automatic zeroing, spanning, and calibrating equipment. In addition, they have the advantage of being linear in output. NDIR systems have the advantages of being insensitive to flow rates, of requiring no wet chemicals, and of being reasonably independent of ambient air temperature changes if the instrument is properly thermostatted. The NDIR analyzer is generally accepted as being the most reliable reference method for the calibration of other instruments.

Continuous CO monitoring instruments based on galvanic and coulometric principles have not been used extensively in field operations. They are flow- and temperature-dependent, and require the use of filters to remove multiple interferences.

The mercury vapor analyzer, which depends on the liberation of mercury vapor when CO is passed over hot mercuric oxide, has been used as a portable, continuous monitoring analyzer with a special capability for measuring low CO concentrations (0.29 mg/m^3 or 0.25 ppm). The instrument does not appear, however, to be suitable for routine CO monitoring of urban atmospheres.

The automated gas chromatographic system is semicontinuous in operation, but has the advantage of measuring both CO and methane. Concentrations of from 0.1 to 1150 mg/m^3 (0.1 to 1000 ppm) may be determined, and instrument output for both gases is linear over the range mentioned. Instruments of this kind may be available soon, and it appears this technique will be useful for measuring CO in heavily polluted areas as well as at remote, relatively clean locations.

CO monitoring systems based on catalytic conversion principles are used widely in enclosed spaces, but their applicability for ambient air monitoring is limited.

Colorimetric (colored silver sols) methods are not recommended for monitoring ambient air. The approach may be useful, however, for measuring CO in stack effluents. Colorimetric techniques and length-of-stain discoloration methods are recommended for use only when the above-mentioned physicochemical systems are not available. They can be used in the field where accuracy is not required and can be of great value during air pollution emergencies.

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CHAPTER 5

ATMOSPHERIC CARBON MONOXIDE CONCENTRATIONS

A. INTRODUCTION

The concentration of carbon monoxide (CO) in urban communities varies considerably with time and location. Continuous monitoring for CO has been conducted at various locations in the United States and in Europe. These efforts and special studies have made it possible to discern some patterns in CO concentration variations.

Statistical analysis techniques have led to the development of methods for analyzing CO concentration data. From CO monitoring information for a given location, the frequency of occurrence of a specific CO concentration can be estimated.

B. TEMPORAL VARIATIONS IN CARBON MONOXIDE CONCENTRATIONS

1. Diurnal Patterns

Community CO levels follow a regular diurnal pattern of variation dependent primarily on human activity (1-10). Ambient CO concentrations generally correlate well with traffic volume: the highest correlations and levels are associated with measurements taken where vehicular traffic is heaviest.

Although the exact shape and magnitude of the diurnal CO curve for a community is dependent to a large extent on meteorologic factors (11), two peaks corresponding with the morning and evening traffic "rush" hours are usually detectable, as shown in Figure 5-1 (12). Carbon monoxide levels in most cities reach their initial daily maximum between 7 and 9 a.m.,

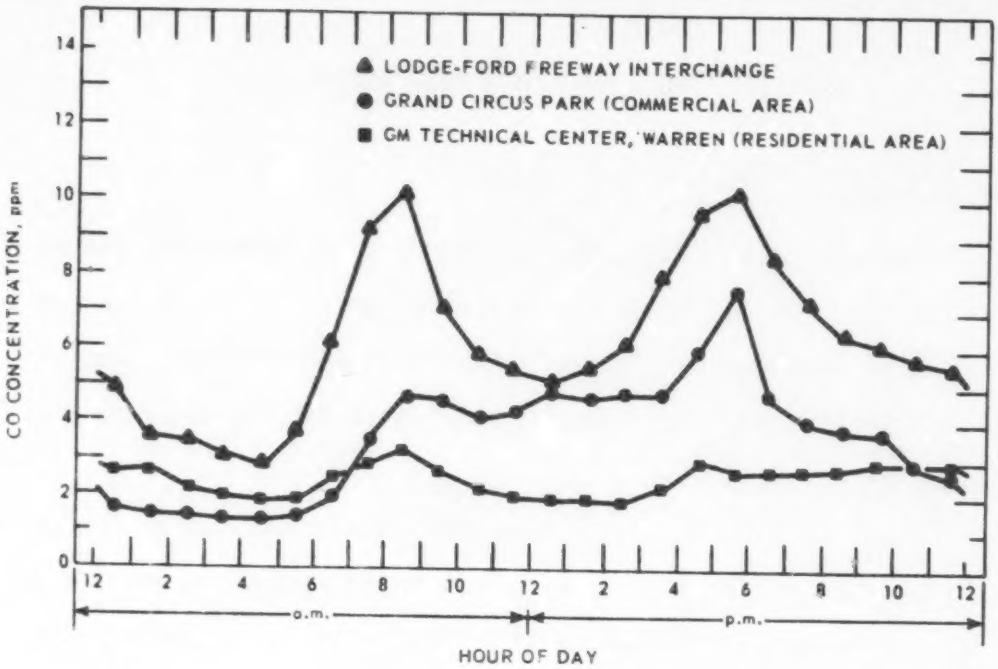


Figure 5-1. Diurnal variations in mean carbon monoxide levels on weekdays in Detroit (12).

coincident with heavy morning automobile traffic. Another peak is reached in the late afternoon and early evening hours (1,2,4,5).

An exception to these general observations may be found in "downtown" New York City, where there is a rapid rise in CO concentration in the morning corresponding to the morning rush hour traffic, followed by a constant plateau that lasts until afternoon when a slower rise begins and builds to a peak in late afternoon (Figure 5-2). The shape of the traffic curve in Figure 5-2 is indicative of saturation levels of traffic (13).

The diurnal pattern within a community, because it is directly related to traffic volume, shows little variation between the days of the week except for weekends and holidays. The weekday concentrations are higher than those recorded on Saturdays, and Saturday concentrations are higher than those recorded

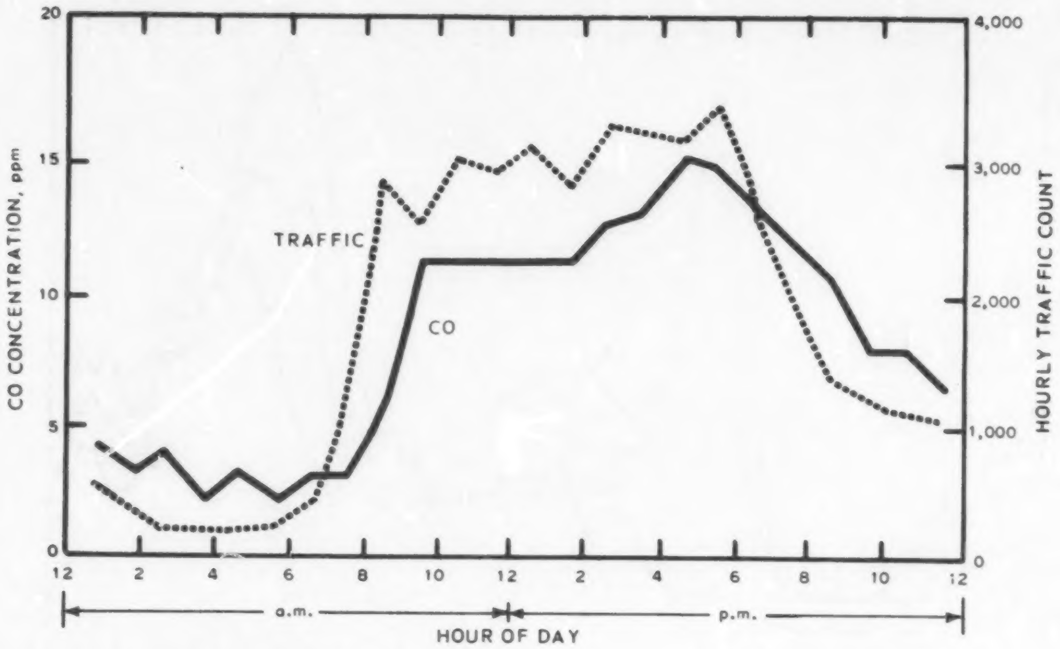


Figure 5-2. Hourly average carbon monoxide concentrations and traffic count in midtown Manhattan, New York City (13).

on Sundays and holidays (2,3). From continuous CO monitoring stations, Georgii (14) found the CO concentrations to be lower on Saturday and Sunday than during the other days of the week. During weekends the CO concentration in German cities seems to reach only one peak, which occurs at about 7 p.m. Late evening and early morning CO concentrations are higher on weekends than on weekdays (Figure 5-3). Collucci and Begeman found that the CO concentration on freeway sites in New York and Los Angeles reached similar levels during weekdays and Sunday (12).

The variation of atmospheric levels of CO with traffic density was studied by Brief, Jones, and Yoder at six locations in a northeastern metropolitan city in the United States (3). Based on 30 data points, the investigators found that CO concentrations showed a linear correlation

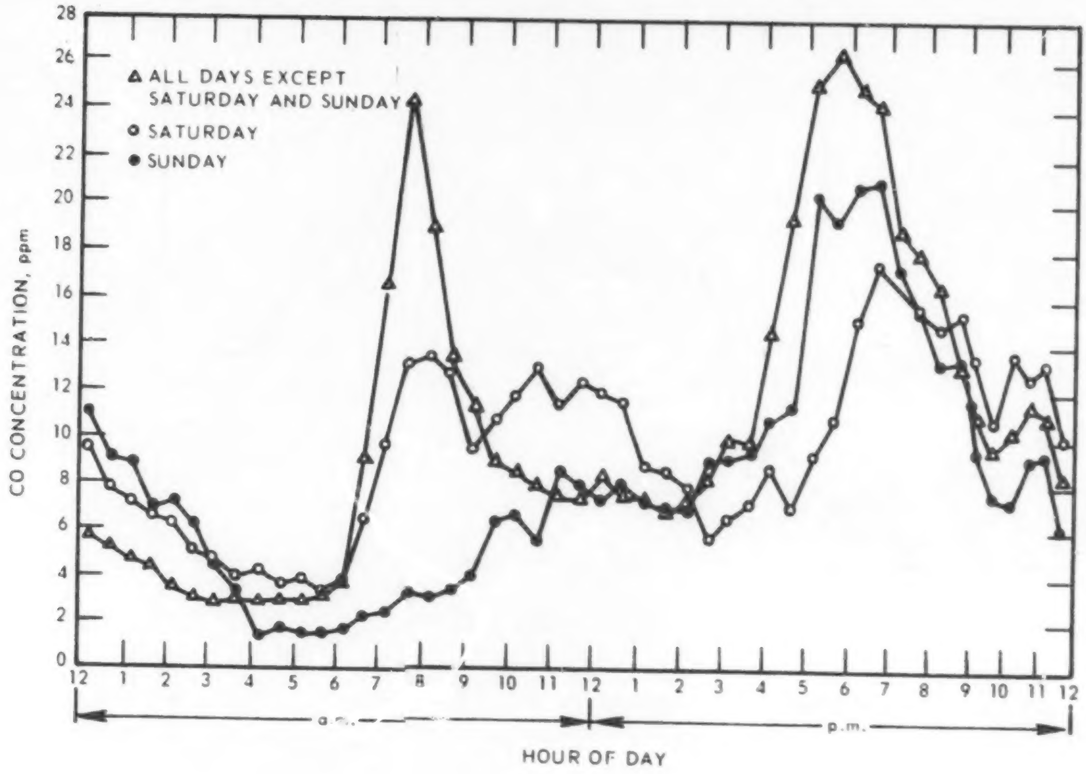


Figure 5-3. Average diurnal concentration of carbon monoxide in Wiesbaden, Germany (Wilhelms Street).

with traffic density. The CO levels were correspondingly lower on Sundays when the average traffic flow was reduced by one-third to one-half the overall weekday average. Figure 5-4 depicts the correlation of CO with traffic density found by these investigators along with the corresponding 95 percent confidence limits of atmospheric CO concentration on traffic density. The extent to which the correlations and confidence intervals can be generalized in other cities varies with such factors as meteorology, type of traffic flow, and the influence of emission sources other than vehicles (3). High wind and vertical turbulence, factors that promote maximum dilution, were not experienced during these tests, but under such conditions the slope of the correlation curve could be lessened so that even under conditions

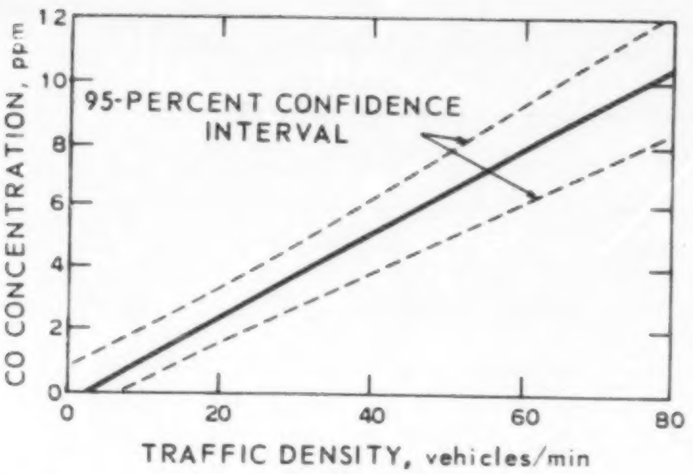


Figure 5-4. Correlation of carbon monoxide concentration and traffic density (3).

of high traffic density the levels of CO might be below the lower confidence limits. On the other hand, the slope of the correlation curve in an area with predominantly stagnant weather conditions might be greater than that shown in Figure 5-4.

In their studies in Detroit, New York, and Los Angeles, Colucci and Begeman found correlation coefficients ranging from 0.75 to 0.95 between CO concentrations and traffic counts (12). Similar analyses have been conducted by others (13,15,16). In Berlin correlation coefficients have been determined for six sites at elevations from 0.75 to 24 m above ground level as shown in Table 5-1 (7,8).

A high correlation has been found between CO concentrations and concentrations of hydrocarbons and lead in a street with heavy traffic (7).

As was indicated in Chapter 3, an increase in average automobile speed in urban driving reduces CO emissions. It should be possible, therefore, for city planners to capitalize on this fact by designing roadways to provide for increased speed and continuity of traffic through central

Table 5-1. CORRELATION COEFFICIENTS BETWEEN TRAFFIC DENSITY AND CO CONCENTRATION AT SIX HEIGHTS (7,8)

Sampling height above ground, m	0.75	1.5	3.0	6.0	12.0	24.0
Correlation coefficients	0.90	0.88	0.89	0.87	0.89	0.88
Average CO concentration, ppm/yr	15.6	14.5	12.4	10.6	9.1	6.1

urban areas as well as providing for a constant volume of traffic.

2. Seasonal Patterns

Community atmospheric CO levels reveal seasonal patterns. U.S. Continuous Air Monitoring Projects (CAMP) data for the years 1964 through 1968 indicate that CO concentrations are generally highest in autumn, followed by summer, spring, and winter, respectively (17). The tendency toward increased atmospheric stability and low wind speeds in autumn and summer contribute substantially to the occurrence of high CO concentrations.

3. Annual Variations

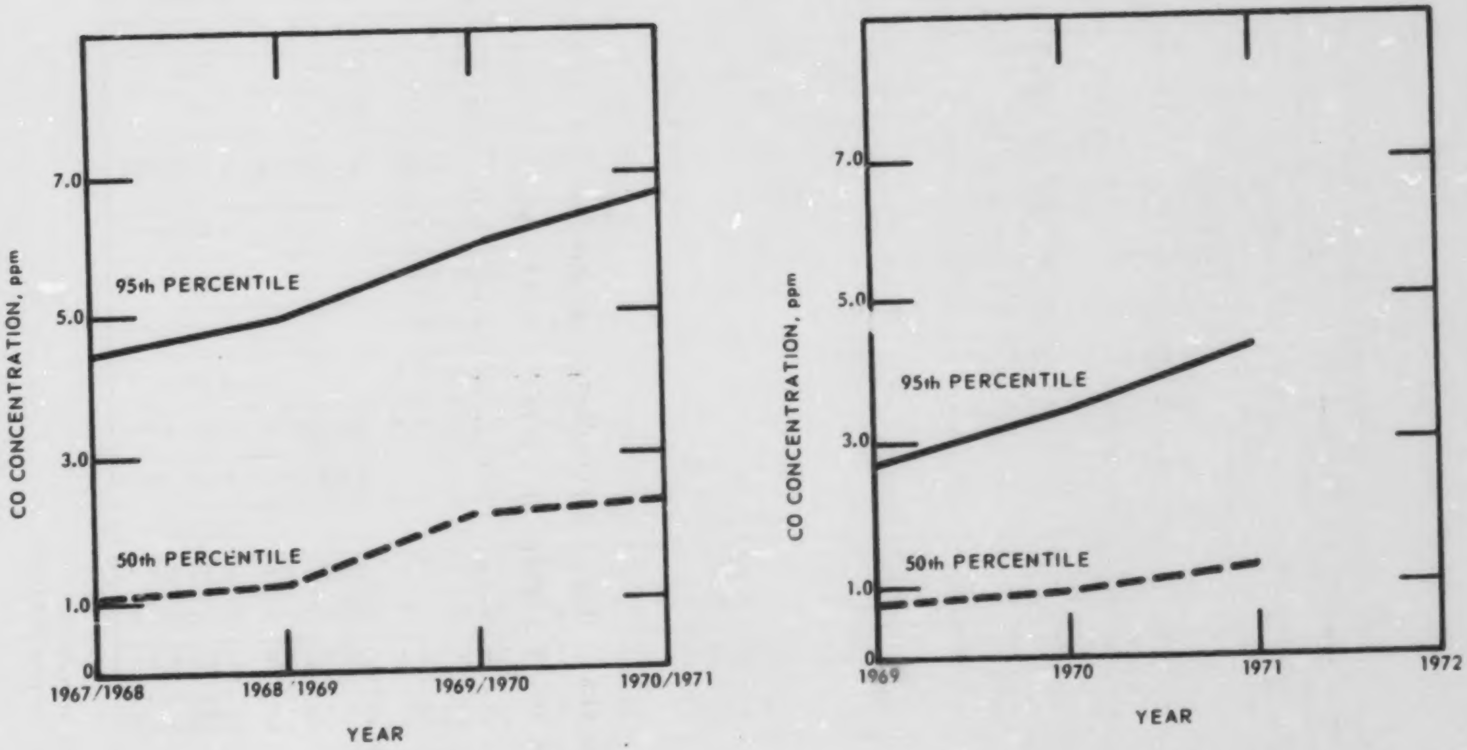
An example of data available for studying differences by year and trends of annual CO concentrations are shown in Table 5-2 (18). Calculations from continuous measurements at 46 sampling sites (located mainly in California) indicate that no essential change in annual average concentrations occurred from year to year. There were average annual changes of 1 mg/m^3 (1 ppm) up or down, but there does not appear to be any consistent upward or downward trend in annual average CO concentrations. Measurements from Frankfurt/Main and Munich point to an increase of CO concentration since 1966 (Figure 5-5).

Table 5-2. CARBON MONOXIDE CONCENTRATION (ppm) AT CAMP* SITES, BY AVERAGING TIME AND FREQUENCY, 1962 THROUGH 1968 (18)

City and averaging time	Annual maximum	1962 through 1968				Maximum for year							Percent data available	Percent of time concentration is exceeded							
		Geom. mean	SGD[a]	Max	Min	1962	1963	1964	1965	1966	1967	1968		0.01	0.1	1	10	30	50	70	90
CHICAGO																					
5 min	81	12.1	1.54	78	43	43	50	64	61	78	63	57	55	56	44	33	21	15	10	6	3
1 hr	53	12.3	1.46	59	28	28	36	46	44	59	56	40	56	51	40	30	21	15	10	7	3
8 hr	38	12.5	1.40	44	20	20	22	35	37	44	33	33	57		34	27	20	14	10	7	4
1 day	32	12.6	1.36	33	16	17	19	27	32	33	23	16	58			25	20	14	10	7	5
1 mo	18	13.0	1.22	21	7	7	10	17	21	18	11	7	62				18	13	10	7	6
1 yr	13	13.2	1.00	17	6			12	17	13		6	57						12		
CINCINNATI																					
5 min	103	4.0	2.09	50	26			26	50	32	47	46	70	40	32	16	9	6	5	3	2
1 hr	52	4.3	1.92	42	20			22	34	20	27	42	71	36	32	15	9	6	5	4	2
8 hr	29	4.5	1.77	36	12			19	21	12	17	36	72		32	14	8	6	5	4	2
1 day	22	4.6	1.69	32	9			17	16	9	13	32	74			14	8	6	5	4	3
1 mo	9	5.0	1.41	11	5			11	5	7	8	8	77				7	6	5	4	3
1 yr	5	5.3	1.00	6	4			6	4	5	5	6	100						5		
DENVER																					
5 min	114	6.4	1.93	90	63				70	73	63	90	72	62	44	26	13	9	8	4	2
1 hr	61	6.7	1.79	79	40				40	55	43	79	72	53	40	24	13	9	6	4	2
8 hr	37	6.9	1.66	30	27				27	29	30	29	74		29	18	12	8	6	5	3
1 day	28	7.1	1.60	21	16				16	20	20	21	76			16	11	8	7	5	4
1 mo	12	7.5	1.35	12	9				10	12	10	9	81				9	8	7	6	4
1 yr	8	7.9	1.00	8	5				7	8	8	5	100						7		
LOS ANGELES																					
5 min	72	9.5	1.58	81	70	81	70	75					79	50	36	25	16	12	10	9	7
1 hr	46	9.7	1.50	47	35	43	35	47					79	43	34	25	16	12	10	9	7
8 hr	32	9.9	1.43	28	27	28	28	27					81		27	21	15	12	10	9	8
1 day	26	10.0	1.39	23	22	22	22	23					82			19	15	12	11	9	8
1 mo	15	10.3	1.24	14	13	14	13	14					89				13	12	11	9	9
1 yr	11	10.6	1.00	11	9	11	9	11					100						11		
PHILADELPHIA																					
5 min	83	6.7	1.77	67	43	51	52	43	67	47	44	49	58	47	35	22	13	9	7	5	3
1 hr	48	6.9	1.66	54	35	47	47	37	54	43	42	35	58	45	33	22	13	9	7	5	3
8 hr	31	7.1	1.56	36	23	36	35	27	26	34	23	26	59		27	20	12	9	7	5	3
1 day	24	7.2	1.50	25	14	23	25	21	19	20	14	23	60			16	12	9	7	6	4
1 mo	12	7.6	1.30	14	9		14	13	11	10	9	11	62				10	8	7	6	5
1 yr	8	7.9	1.00	8	6			7	8	7	6	8	71						7		
ST. LOUIS																					
5 min	50	5.4	1.65	68	45			45	53	68	60	47	86	42	30	19	10	7	5	4	2
1 hr	31	5.6	1.56	29	25			25	27	29	27	26	87	27	22	17	10	7	5	4	2
8 hr	21	5.7	1.48	18	12			18	18	18	14	12	88		17	13	9	7	5	4	3
1 day	17	5.7	1.43	17	9			17	15	12	11	9	89			12	9	7	6	5	3
1 mo	9	6.0	1.28	9	6			9	9	8	8	6	95				8	6	5	5	4
1 yr	6	6.1	1.00	6	5			6	6	6	6	5	100						6		
SAN FRANCISCO																					
5 min	39	4.7	1.62	40	38		38	40					67	27	20	14	9	6	5	4	2
1 hr	25	4.8	1.53	38	22		38	22					68	20	18	13	8	6	5	4	2
8 hr	17	4.9	1.46	18	14		18	14					68		13	11	8	6	5	4	3
1 day	14	5.0	1.41	14	10		14	10					69			9	7	6	5	4	3
1 mo	7	5.1	1.25	7	6		6	7					67				6	6	5	5	4
1 yr	5	5.3	1.00	5	5			5					50						5		
WASHINGTON																					
5 min	87	3.4	2.10	59	29	30	44	29	49	47	37	59	71			27	8	5	4	3	1
1 hr	44	3.6	1.93	41	25	25	41	28	32	38	32	27	71	35	27	17	8	5	4	3	2
8 hr	25	3.7	1.78	34	17	19	34	18	17	22	23	21	72		22	15	8	5	4	3	2
1 day	18	3.8	1.70	23	11	14	23	13	11	15	15	14	73			13	8	5	4	3	2
1 mo	7	4.2	1.41	10	5	7	10	6	6	5	7	7	76				7	5	4	3	2
1 yr	4	4.4	1.00	7	3		7	6	4	3	5	3	86						4		

[a] Standard geometric deviation

*Continuous Air Monitoring Projects.



a. Winter half-year.

b. Summer half-year.

Figure 5-5. Trends in CO concentrations in winter (a) and summer (b) half-years in Frankfort/Main, Germany (6).

C. EFFECT OF METEOROLOGICAL FACTORS

The rate of emission and dispersion determines the ambient concentration of a pollutant at a given location. Both macro- and micrometeorological factors play a role in the rate of dispersion of CO emissions. For dispersion over short distances, microscale factors are most important (1,15), but macroscale factors dominate over extended distances. The fundamental meteorological factors involved in dispersion are wind speed, wind direction, turbulence, and atmospheric stability. The largest single source of CO in the urban environment is the automobile. Thus, the greatest CO emissions are expected to be found on city streets when traffic volume is high. On downtown city streets where masses of people are close to emission sources, the micrometeorological factors become critical in determining human exposure to carbon monoxide.

Because automobiles usually are moving and creating their own rather small, but intense, field of mechanical turbulence, the resulting atmospheric diffusion of CO is important in the determination of CO concentrations near the traffic flow. This is particularly true when the wind speed is low (mean wind speed of $\leq$ 1.3 m/sec or 3 mi/hr) (11,15). When there are high wind speeds, the air flowing over and around buildings adds turbulence and mixing to that generated by vehicles. Higher wind speeds, therefore, increase turbulence and dilution, and thereby cause generally lower pollutant concentrations.

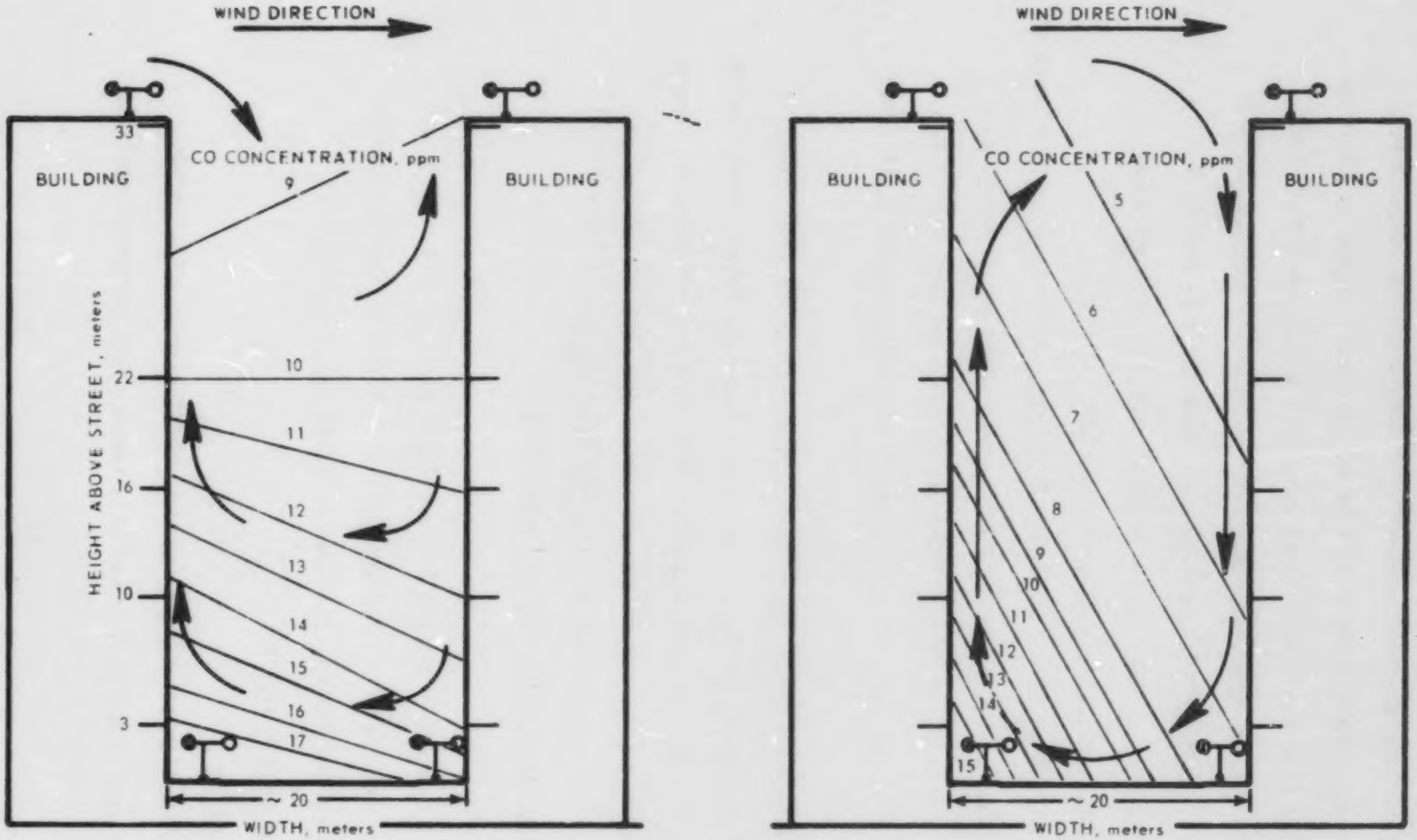
Two characteristic types of diffusion patterns were found in urban streets in Frankfurt (6). The meteorological vortex at wind speeds of less than 2 m/sec

(4.5 mi/hr) is relatively ineffective (Figure 5-6a). As can be seen, the CO concentration is nearly homogeneous in the horizontal cross section with a nearly logarithmic decrease of CO concentration with height above the street. Higher wind speeds increase turbulence and diffusion, but lower concentrations are found only on the downwind side of the street. On the upwind side, the concentration of CO was found, on the average, to be nearly as high as at low wind velocities as shown in Figure 5-6b (19).

During prolonged periods of air stagnation, which occur periodically in most urban communities, poor or inadequate diffusion contributes to the buildup of atmospheric levels of CO and other air pollutants. In the autumn of 1964, during unusually prolonged and severe inversions, CO concentrations in Los Angeles and in Sacramento, California, exceeded 35 mg/m^3 (30 ppm) for 8 hours (20).

During an air pollution stagnation episode in December 1968, Fett and Lahmann (21) found unusually high CO concentrations at a continuous air monitoring station in Berlin. The site was located in a residential area some distance from the center of the city. On December 9, 1968 the CO concentration reached a geometric average of 23.5 mg/m^3 (20.5 ppm) for approximately 10 hours.

In the results of atmospheric sampling in London from October 1956 to October 1957, Lawther et al. reported a peak CO reading of 270 mg/m^3 (235 ppm) measured on a traffic island and 415 mg/m^3 (360 ppm) of CO measured on a calm day at another street-level location (22). In 1967, of 15,216 samples from 317 locations in Paris, 235 exceeded 115 mg/m^3 (100 ppm) CO. Of these, 11 were equal to or greater than 345 mg/m^3 (300 ppm), 21 were between 230 and 345 mg/m^3 (200 and 300 ppm), and 203 were between 115 and 230 mg/m^3 (100 and 200 ppm) (23).


WIND DIRECTION
BUILDING
CO CONCENTRATION, ppm
BUILDING
33
22
16
10
3
HEIGHT ABOVE STREET, meters
9
10
11
12
13
14
15
16
17
~ 20
WIDTH, meters
WIND DIRECTION
BUILDING
CO CONCENTRATION, ppm
BUILDING
5
6
7
8
9
10
11
12
13
14
15
~ 20
WIDTH, meters

a. Wind speed <2 m/sec.

b. Wind speed > 2 m/sec.

Figure 5-6. Effect of wind speeds <2 m/sec (a) and >2 m/sec (b) on carbon monoxide concentrations at different heights above a downtown "canyon" street (19).

Because smog is indicative of stagnant air conditions, a comparison of CO levels on smoggy and nonsmoggy days is of interest. Based on sampling in a moving vehicle with the intake level about 1.5 meters or 5 feet above the street, Castrop et al. (24) reported that the mean CO concentrations at street level were 11.1 mg/m^3 (9.7 ppm) CO for nonsmoggy days and 45.3 mg/m^3 (39.4 ppm) for smoggy days. The highest concentration detected, 135 mg/m^3 (160 ppm), occurred during a smog period.

A similar analysis of CO measurements from stationary sites in a Los Angeles industrial area showed that the average CO concentration on 21 smoggy days (defined by a 1-hour oxidant concentration equal to or greater than 0.15 ppm) was 13.2 mg/m^3 (11.5 ppm) versus 6.9 mg/m^3 (6 ppm) recorded on 16 smogless days (12).

The concentration of CO in the vicinity of a particular city street is the product of emissions not only on that street but also from streets upwind. Accordingly, the "background" concentration from more distant sources depends for the most part on the number of streets upwind that act as CO sources and on the macrometeorological factors mentioned previously.

D. OBSERVED URBAN CARBON MONOXIDE CONCENTRATIONS

1. Sources of Data

Continuously recorded CO data are available for selected cities in the United States from metropolitan monitoring stations of the Continuous Air Monitoring Projects (CAMP), as shown in Table 5-2.

2. Techniques of Data Analysis

a. Introduction

The collection of air quality data is of little value unless these data are properly analyzed. For this reason, the method of analysis should be clearly defined.

The purpose of data analysis techniques is threefold: to indicate those data parameters frequently used to describe aerometric measurements, to suggest a means of organizing the data in order to arrive at the aforementioned parameters, and to present an air quality model that makes use of these parameters and statistical considerations to extract as much information as possible from the data at hand.

b. Averaging Time

The air quality of an area is estimated by analysis of the pollutant concentrations taken at specific locations over a selected period of time. Each recorded measurement of concentration is indicative both of the absolute magnitude of the actual concentration and of the response time of the instrument. Because of the response time of the instrument, any single, recorded concentration is, of necessity, an average concentration over the time interval of the measurement.

CO measurements are based on either spot or integrated measurements taken over a variety of sampling-time periods. It is necessary, therefore, to arrive at a uniform averaging time based on two basic considerations:

1. The need to compare concentrations measured at different sampling sites.
2. The need to select an averaging time meaningful to the effects produced by the pollutant.

The minimum averaging time is a parameter of the particular instrument used. The resulting data, however, may be reported on the basis of any averaging time equal to or greater than this minimum value. For example, the nondispersive infrared CO analyzer (NDIR) senses and measures on a continuous basis, but only records an instantaneous measurement once every 5 minutes. The 12 consecutive 5-minute measurements within an hour may then be averaged to give the 1-hour averaging time value.

An averaging time of 8 hours is frequently used for the presentation of CO concentrations. At low atmospheric CO concentrations, such as those found in community air, from 4 to 12 hours is required for the carboxyhemoglobin levels in the human body to reach equilibrium with the average concentration of CO being inspired. Because of man's slow absorption and desorption of CO at low concentration levels, short-term concentrations are of less interest than are 8-hour average values. It must be recognized, however, that short-term high-level concentrations may be important from a health standpoint. One disadvantage of an averaging time of 8 hours is that CO concentrations during rush hours, which last about 3 hours, can not be adequately assessed.

c. Frequency Distribution

Use of a frequency distribution is a common method of reducing a set of data to a consistent averaging time. The advantage in using such a technique is that it provides an estimate of the probability of occurrence of a given CO concentration. This feature is important in assessing the severity of pollution. Moreover, certain frequency distributions have been well studied and lend themselves to statistical analysis. The frequency distribution of the available data can then be used to determine whether one of these common distributions may be fitted, thereby facilitating the extraction of statistical parameters of the data.

Most samples of atmospheric pollution concentrations have been found to exhibit a log-normal frequency distribution. Simply stated, this implies that the logarithms of the concentrations have a gaussian (normal) distribution; therefore, the wealth of statistical techniques used with normally distributed data may be applied as well to the logarithms of aerometric data.

One such technique involves the use of probability paper to graphically depict a distribution under consideration. When the cumulative frequency distribution of a collection of air quality measurements is plotted on log-versus-normal-probability paper, the resulting curve can usually be approximated by a straight line. The concentration at the 50 percent mark, representing the arithmetic median value, is termed the geometric mean. Theoretically, measured concentrations will be below this value half of the time and half of the time they will be above it.

For a log-normal distribution, the geometric mean is a measure of central tendency. Similarly, the 84.13 percentile value divided by the 50.00 percent value (geometric mean) is termed the standard geometric deviation and is a measure of the dispersion of the data. Knowing these two values permits determination of the entire distribution.

The arithmetic mean of log-normally-distributed air-quality measurements is always larger than the geometric mean. The arithmetic mean, m, may be calculated (25) from the geometric mean, M_g, and standard geometric deviation (σg), by means of the following equation:

$$\log m = \log M_g + 1.151 (\log \sigma g)^2$$

All of the CAMP data for the periods 1962 through 1968 have been analyzed to give concentration as a function of averaging time and frequency. Examples of the types of summaries that may be extracted from these data are shown in Table 5-2. The magnitude of CO concentrations greater than the geometric mean tend to decrease with an increase in averaging time whereas the magnitude of concentrations less than the geometric mean tend to increase with an increase in averaging time. Similarly, the geometric mean concentration for any averaging time tends to remain relatively constant. These trends are inherent in the averaging process and result in a decrease in the dispersion of the concentration values as the time over which these concentrations are averaged increases. As would be expected, this decrease in dispersion is reflected in a decrease of standard geometric deviation as averaging time increases.

d. An Air Quality Model

Certain trends become apparent when the frequency of occurrence of various CO concentrations and their variability with averaging time are examined. In an extensive analysis of urban pollution data, Larsen (26) has found that:

1. Concentrations are approximately log-normally distributed for CO and other pollutants in all cities for all averaging times.
2. The median concentration (50th percentile) is proportional to the average time raised to an exponent.

These two factors greatly simplify the analysis of aerometric data. The former implies a common form of distribution of concentrations that is independent of geographic location and amenable to statistical analysis. Such a distribution plots as a straight line on a log-versus-probability scale; the distribution, therefore, may be defined by relatively few points. The latter factor implies that once the distribution of concentrations for one averaging time is known, then distributions for other averaging times can be calculated.

These characteristics of the measurement data have been used to build a statistical model expressing air pollution concentration as a function of averaging time and frequency. The accuracy of this model in depicting the expected air quality of a region depends on certain characteristics of the sampling data input; the larger the sample and the closer the sample data meets the two conditions cited above, the more accurately will the model simulate reality. (Because of the strong dependence of this model on the assumption of log normality and the ease with which a data set may be checked for exhibition of a log-normal distribution, i.e., the use of the log-versus-normal-probability paper, it is wise to check any data set against this assumption before applying the model.)

Two values of air quality, the 1-hour-averaging-time concentration that is exceeded 0.1 percent of the time and the 1-hour-averaging-time concentration that is exceeded 30 percent of the time, are used to produce a model that best depicts the most polluted half of the air samples, which are of greatest interest. One-hour averaging times are used because the model is general for gaseous air pollutants and the response times for some air-sampling instruments (such as those for nitrogen oxides) may be as long as half an hour (thus causing errors in concentration measurements averaged over less than 1 hour). Another reason is that more data averaged over 1 hour are available than for any other averaging period.

Maximum air pollutant concentrations within a community (including CO) may vary markedly from year to year. The maximum measured in a particular year in a particular community may be twice the maximum measured in another year. This is the case in Chicago, Cincinnati, and Washington (Table 5-2), where the maximum 8-hour concentration measured in each of these cities in the most polluted year is about twice the maximum concentration measured in the least polluted year. The developed statistical model has been used to calculate the maximum concentration predicted to occur on the average of once a year, i.e., the calculated annual maximum 8-hour concentration. For any averaging time, although observed year-to-year mean and peak CO values may vary markedly within any community, the calculated annual maximum value remains constant.

3. Special Carbon Monoxide Exposure Situations

a. Variations with Type of Vehicle Traffic

Larsen and Burke (27) have analyzed aerometric CO data from a variety of sampling locations in many cities using the frequency distribution described earlier. These studies included data from various cities of the continuous air monitoring networks, commuter traffic surveys, and special studies. The data were treated so as to calculate on a uniform basis the maximum 8-hour averaging time concentrations to be expected annually. This was done for values measured in the following situations:

1. Vehicles in downtown traffic.
2. Vehicles on expressways or arterial routes.
3. Residential-commercial areas.
4. Mixed industrial areas.
5. Commercial areas.
6. Residential areas.

The results are shown in Figure 5-7.

Studies of the first two types of exposure have been conducted (28-42). The average citizen is not often subjected to the first two types of exposure for 8 hours. Nevertheless, cab drivers, bus drivers, delivery truck drivers, and some policemen are so exposed. A number of epidemiclogical studies on occupationally exposed groups are discussed in Chapter 8.

Figure 5-7 shows that, if the most polluted 5 percent of the off-street central urban areas represented by the commercial classification were selected, then the maximum 8-hour annual concentration would approximate 36 mg/m^3 (40 ppm). The CO concentrations expected inside the passenger compartment of motor vehicles on city streets in heavy traffic at the most polluted 5 percent of the locations would be almost 3 times this level, or 132 mg/m^3 (115 ppm). In vehicles travelling on expressways or arterial routes, the value would be 85 mg/m^3 (75 ppm), and in residential or suburban areas the value would be about 26 mg/m^3 (23 ppm). The CO concentrations in downtown traffic appear to be about 5 times

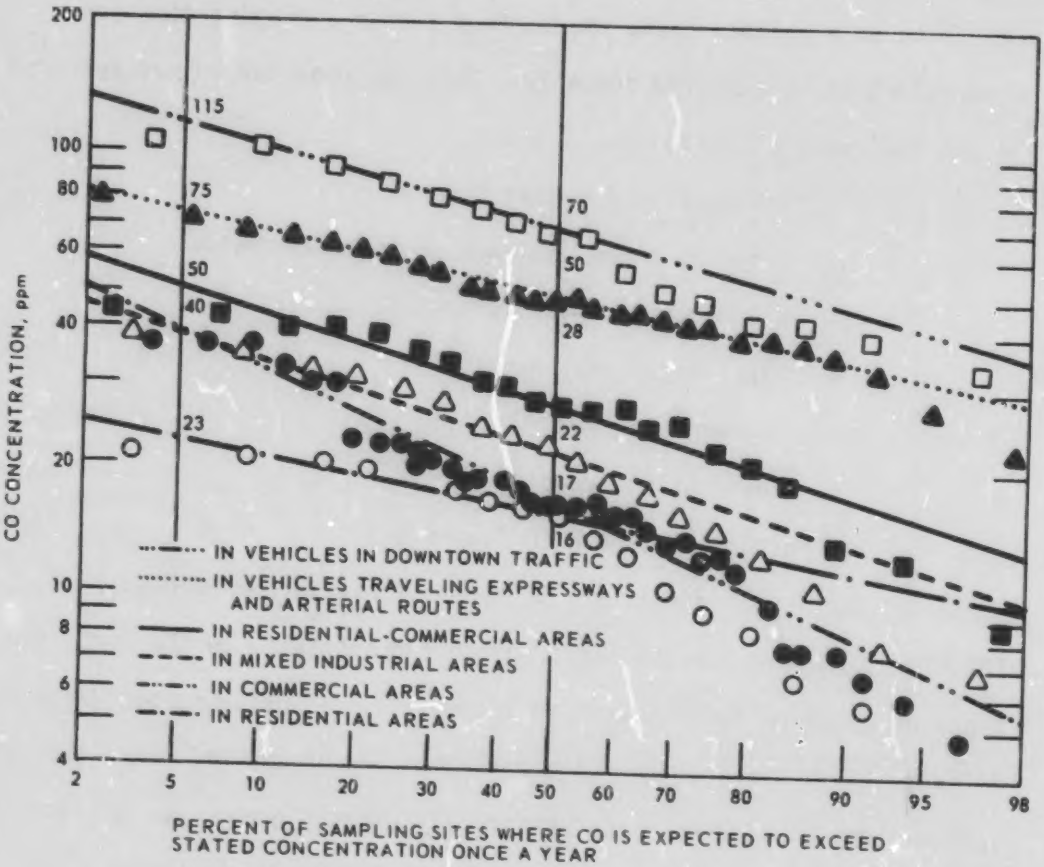


Figure 5-7. Maximum annual 8-hour-averaging-time concentrations of carbon monoxide expected at various types of sites.

those found in residential areas. Similar findings reported by Colucci and Begeman are illustrated in Figure 5-1.

b. Car Passenger Exposure to Carbon Monoxide

Each working day a sizeable segment of the population spends considerable time driving in traffic of varying density. During that time most vehicle occupants are exposed to higher concentrations of CO than they would otherwise encounter.

The results of a study of driver exposure to CO for 20- to 30-minute periods over various driving routes are given in Table 5-3 (4,30).

Table 5-3. IN-TRAFFIC 20- TO 30-MINUTE CARBON MONOXIDE EXPOSURES FOR VARIOUS DRIVING ROUTES

City	Date	Center city routes					Arterial routes					Expressway routes				
			Average CO concentrations, ppm					Average CO concentrations, ppm					Average CO concentrations, ppm			
		No. runs	Min.	Avg., all runs	90th percentile	Max.	No. runs	Min.	Avg., all runs	90th percentile	Max.	No. runs	Min.	Avg., all runs	90th percentile	Max.
Atlanta	May 11–17, 1966	7	13	21	27	27	9	21	30	38	40	10	12	23	33	35
Baltimore	April 8–15, 1966	14	15	24	34	38	25	6	17	29	33	18	2	9	19	21
Chicago	May 25–June 8, 1966	17	24	32	40	55	51	7	16	21	31	31	13	24	34	37
Chicago	Feb 27–Mar 17, 1967	10	19	34	50	53	28	1	16	27	41	35	3	20	31	35
Cincinnati	Aug 2, 16, 17, 1966	8	17	29	48	50	25	3	17	26	32	7	3	10	15	15
Cincinnati	June 1967	6	12	20	32	32	11	9	15	19	19	24	7	15	24	34
Denver	Sept 19–30, 1966	10	21	34	49	54	41	11	32	47	61	24	10	21	33	38
Detroit	June 13,–July 14, 1966	16	15	25	35	36	51	14	25	33	41	48	11	25	33	54
Houston	Dec 5, 1966–Jan 29, 1967	14	16	38	60	70	23	5	15	28	33	31	2	16	33	39
Louisville	Mar 1–4, 1966	10	16	23	33	33	14	4	16	26	31	14	2	8	15	21
Los Angeles	Oct–Nov 3, 1966	17	27	40	59	60	15	24	38	58	60	87	9	29	47	62
Minneapolis-St. Paul	Aug 29–Sept 9, 1966						59	10	23	36	41	No expressway runs				
Minneapolis	Aug 29–Sept 9, 1966	15	20	30	44	45										
St. Paul	Aug 29–Sept 9, 1966	13	21	35	58	65										
New York	April 21–May 5, 1966	48	14	32	44	58	No arterial runs made					31	8	23	36	45
New York	May 1–31, 1967	30	9	27	39	42	No arterial runs made					17	5	21	38	39
Philadelphia	June 1–16, 1967	20	18	29	37	38	40	9	22	35	38	20	8	17	28	38
Phoenix	Nov 9–18, 1966	12	27	38	53	54	26	13	27	37	43	39	12	23	34	50
St. Louis	Feb 6–17, 1967	19	15	28	45	50	38	8	17	23	34	37	2	10	17	22
Washington	April 5–27, 1967	34	8	26	42	63	17	10	20	29	30	35	2	12	26	33
All	Mar 1966–June 1967	320	8	30	44[a]	70	473	1	22	33[a]	61	508	2	18	29[a]	62

[a] Estimated.

The results indicate that exposure levels vary with vehicular route. Average CO concentrations were highest on center city routes, somewhat lower on arterial routes, and lowest on expressway routes.

c. Severe Carbon Monoxide Exposure Locations

Although significant concentrations of CO, which affect large subgroups of the population, occur on city streets, even higher concentrations, often exceeding 100 mg/m^3 (84 ppm), have been reported in underground garages, tunnels, and loading platforms (9,34-36).

A survey was conducted by the National Air Pollution Control Administration (NAPCA) at the Chicago Post Office in the Air Rights Building, which is built over a four-lane vehicle expressway. Preliminary results indicate that CO concentrations ranged from 17 to 89 mg/m^3 (15 to 77 ppm) at the east loading platform of the building with an average concentration of 47 mg/m^3 (41 ppm). The west loading platform showed CO levels that ranged from 9 to 75 mg/m^3 (8 to 65 ppm) with an average of 28 mg/m^3 (24 ppm). Other locations and rooms had lower CO concentrations (37).

Chovin (9) has recorded average CO levels of 170 mg/m^3 (150 ppm) between 7:30 and 8:00 a.m. and 210 mg/m^3 (180 ppm) between 7:30 and 8:00 p.m. in the air of a Paris police garage. Georgii found maximum CO concentrations of more than 230 mg/m^3 (200 ppm) and average CO levels around 58 mg/m^3 (50 ppm) at rush hour periods in a public garage in Frankfurt/Main (43).

Trompeo et al. (38) measured the CO levels in 12 underground garages in Rome. The average CO level based on 132 readings was 113 mg/m^3 (98 ppm), ranging from a minimum of 12 mg/m^3 (10 ppm) to a maximum of 350 mg/m^3 (300 ppm). Forty-two percent of the readings showed CO levels equal to or greater than 115 mg/m^3 (100 ppm).

Waller et al. (34) reported on CO concentrations in the Blackwell and Rotherhithe Tunnels in London during periods of high traffic volume. The mean CO concentrations during the morning and evening "rush" hours were slightly more than 115 mg/m^3 (100 ppm). Although the usual sampling periods were short, one of the sampling periods in the Rotherhithe Tunnel exceeded 1.75 hours. This study indicated that peak CO levels reached 600 mg/m^3 (500 ppm) at midnight on a Sunday; other peaks were 500 mg/m^3 (450 ppm) on a Friday evening and 390 mg/m^3 (340 ppm) on a Saturday evening. (The fans in these tunnels were shut off during the night, thereby reducing ventilation.) Wilkins reported earlier that CO concentrations in the Blackwell Tunnel ranged from 170 to 680 mg/m^3 (150 to 590 ppm) in September 1954. Other air samples taken in this tunnel between June and December 1955 showed CO levels ranging from 270 to 540 mg/m^3 (235 to 470 ppm) CO during the morning rush hours (39).

d. Indoor Levels of Carbon Monoxide

Carbon monoxide found inside buildings may be attributable to internal sources such as space heating units and cooking stoves as well as to sources outside the building (44).

In 1969, NAPCA supported a preliminary study of the contribution of both outdoor and indoor sources to levels of CO in single-family homes (45) This study showed that the major source of CO in a house with gas-burning devices was inside the house, although between 8 and 10 p.m. on Friday an outdoor source was dominant.

e. Projected Future Trends

A number of studies and calculations of future CO emissions and concentrations have been made from urban traffic data; other studies are in progress. Ott et al. (40) calculated present and future CO emissions and ambient CO concentrations in Washington, D.C., using 1964 and projected 1985 traffic volumes and emissions factors with a meteorological diffusion model. They found that: 1) with no emission control, the total CO emitted in Washington will approximately double in a nonuniform manner; the smallest increases will occur downtown and the greatest increases in the outskirts; 2) the principal effect of such nonuniformity, also apparent in Chicago, is to increase the area of the city exposed to high emission densities, leading to consequent increases in the area over which higher concentrations occur; 3) without control, the mean annual CO concentrations at four selected sites in Washington would range from 2.5 to 12.6 mg/m^3 (2.2 to 11.0 ppm) in 1985, representing increases of from 44 to 69 percent over the 1964 values.

A corollary to the second finding above is apparent. If the area of a city subjected to high pollutant concentrations is increased, the population in some downwind parts of that area will be exposed to high concentrations for longer periods of time than previously because cleaner air has to come from farther away. The probability of exceeding a given 8-hour-average CO concentration is, therefore, increased; or, conversely, the 0.1 percentile level in Larsen's model (26) will be higher.

Taking the increase presented in the third finding above to be about 50 percent implies that if maximum urban concentrations approximated 45 mg/m^3 (40 ppm) in 1965, and if CO from motor vehicles were not controlled, concentrations of about 70 mg/m^3 (60 ppm) would be expected in 1985. In-vehicle concentrations of at least twice this level, or 140 mg/m^3 (120 ppm), would be expected. It should be pointed out that future levels of CO in metropolitan areas are highly dependent upon regulations for the control of CO emissions.

E. METEOROLOGICAL DIFFUSION MODELS

Emissions data provide a general idea of the presence of certain pollutants in a given area and may be thought of as showing the potential for exceeding an atmospheric concentration. Whether this potential is realized depends strongly on meteorological factors. These factors have, consequently, been the subject of much study. Simple meteorological indices, such as the number and persistence of low-level inversions per year, give some indication of the frequency with which unfavorable meteorological conditions occur in a particular region. In recent years much effort has gone into the development of relatively complex models that permit a quantitative estimation of the effects of weather on the dispersion of the pollutants (40-43, 46-50). Georgii et al. (6) studied CO concentrations in Frankfurt/Main. The summarized results are:

1. The temporal pattern of CO emission and CO concentrations in ambient air is highly determined by traffic density.
2. In cities CO concentration distributions, both lateral and vertical, are largely dependent on wind speed and direction relative to building configuration as shown in Figure 5-6 (19).
3. Highest concentrations are measured during periods of rush hour traffic that occur during periods of minimal atmospheric dilution.
4. Wind flow above rooftop level is effective at street level only at speeds greater than 2 m/sec (4.5 mi/hr); at wind speeds greater than 5 m/sec (11 mi/hr) at roof height, a complete mixing of the street air takes place.
5. Even at high wind speed above rooftops, the effect of wind direction is that high CO concentrations are produced on the leeward sides of buildings (Figure 5-6).

The mathematical-meteorological model is a useful tool with which to examine the atmospheric impact of the various sources of CO. Although much information may be obtained from such a model, the user should be aware of the nature and limitations inherent in the particular model he has chosen for use. For example, the relative frequency of occurrence and the averaging time of predicted concentrations along with limitations imposed by terrain are integral parts of every model. Such features must be evaluated before application.

The input to all diffusion models consists of emission and meteorological parameters. Normally, the former category includes pollutant emission rates and source heights, and the latter includes wind velocities and those parameters that determine atmospheric dispersion. The output from these models is usually in the form of a pollutant concentration at specified locations. The gaussian diffusion equation is the most widely accepted of its type and forms the basis of most models. Turner has described this equation and its use (51).

The modelling of CO emission and dispersion is complicated by the fact that the chief source of CO, the motor vehicle, is a multiple emission source and is mobile, rather than a source at a fixed point. The use of CO in diffusion models also simplified some aspects of the modelling effort, however. Since automotive-generated CO is usually of primary concern, source height may be considered as constant at ground level. Also, no consideration of effective residence time, i.e., removal rate of CO, is required because of the assumed stability of this pollutant in an urban environment. By incorporating assumptions about the way traffic flows and distributes the CO over particular routes or throughout the city into a model, it is possible to apply a simulation approach to this pollutant.

These models are usually used to estimate concentrations for one source-receptor pair at a time. In order to estimate the air quality at a chosen location, it is necessary to perform a large number of these individual calculations and sum the results. Additionally, the air quality of a region is determined by examining the concentrations predicted for many individual points. Because of the magnitude of the number of calculations to be performed, electronic data processing is almost always needed.

In order to evaluate the accuracy of a given model, the general practice has been to compare measured concentrations at a particular receptor location with those predicted by the model. The model is usually then "calibrated" with respect to these measured concentrations. For CO, diffusion models usually predict concentrations within 0.5 to 0.1 of those measured at the monitoring station (40,51-58). This difference is attributed to the effect of street traffic near the station, which is not allowed for in these models. In addition, although not nearly as important, some part of the concentrations measured in urban areas may be contributed by nonautomotive sources or by meteorological transport of pollutants from other cities. This factor also is not recognized in these models. These variables, therefore, must be accounted for in the application of such models.

In using atmospheric diffusion models, meteorologists have been called on mostly to provide estimates of seasonal or annual mean CO concentration distributions over urban areas, where spatial scales of 1 to 100 kilometers (0.6 to 62 miles) are of primary interest. For these applications, the CO emission inventories available as input to the diffusion model permit only a relatively large-scale or gross treatment of the data. The local effects connected with travel distances of less than 1 kilometer are determined predominantly by aerodynamic or micrometeorological mechanisms, rather than atmospheric diffusion and transport or macrometeorological mechanisms.

F. SUMMARY

Diurnal, weekly, and seasonal patterns of CO concentrations correspond to man's pattern of activities and to meteorological factors. Since urban CO concentrations generally correlate with the community traffic volume, there are usually two peaks in concentration corresponding to the morning and evening rush hours. Peak concentrations are higher on weekdays than on weekends and holidays because of the greater weekday rush-hour traffic volume. Distinct seasonal patterns are primarily the result of both traffic and meteorological variables; the mean concentration of CO is generally higher in autumn and summer than in spring and winter.

Both macro- and micrometeorological factors affect the rate of dispersion of ambient CO. The former is a predominant factor in areawide dispersion; the latter, in local dispersion. Atmospheric stability and wind speed are important macrometeorological factors; mechanical turbulence produced by automobiles and airflow around buildings is an important micrometeorological factor.

Because of physiological considerations, the averaging time of most interest for CO is 8 hours. A statistical model has been developed to convert CO aerometric data based on various averaging times to data based on a uniform 8-hour-averaging time. Based on probability theory, the 0.1 percentile 8-hour-averaging time of CO concentrations approximately represents the worst 8-hour period to be expected in a year. An analysis of air monitoring data indicates that 0.1 percentile 8-hour-averaging-time urban CO concentrations vary from approximately 12 to 46 mg/m^3 (10 to 40 ppm). Analyses of CAMP data suggest that these 0.1 percentile values averaged about 3 times the corresponding median annual CO values.

A statistical analysis of CO aerometric data from 30 technical papers was made. The data were reviewed in order to calculate on a uniform basis the maximum 8-hour-averaging time concentrations expected annually. From these calculations, it is estimated that, for the most polluted 5 percent of the urban sites, the maximum annual 8-hour average in commercial areas would approximate 46 mg/m^3 (40 ppm); in motor vehicles in downtown traffic it would approximate 132 mg/m^3 (115 ppm); and in vehicles on expressways or arterial routes the value would be about 85 mg/m^3 (75 ppm). The CO concentrations in heavy traffic in city streets were almost 3 times the CO levels found in the central urban areas, and 5 times the CO levels found in residential areas.

Concentrations exceeding 100 mg/m^3 (87 ppm) have been measured in underground garages, in tunnels, and in buildings constructed over highways.

Using emission and meteorological data, diffusion models are capable of estimating CO concentrations at a particular receptor point, thus enabling the evaluation of community air quality under a variety of conditions.

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CHAPTER 6

EFFECTS OF CARBON MONOXIDE ON PLANTS AND CERTAIN MICROORGANISMS

A. GENERAL DISCUSSION

Plants are relatively insensitive to carbon monoxide (CO) at the lower levels of concentrations that have been found to be toxic for animals. Much of the early research on the effects of CO on plants was motivated by the assumption that the phytotoxicant in smoke and illuminating gas was CO and the knowledge that plants may be sensitive to some air pollutants at concentrations that do not affect animals. Knight and Crocker (1) were the first to demonstrate that ethylene was the effective contaminant in smoke and illuminating gases and that CO had little or no effect on plants. Much of the early literature referred to studies with impure or undetermined sources of CO. Carr(2), who reviewed the literature published prior to 1961, concluded that CO was not particularly toxic to plants. Although plant injury from CO and ethylene was similar, 5,000 times more CO than ethylene is required to cause injury.

Most of the work on effects of CO on plants was done in the 1920's and 1930's at Boyce Thompson Institute, where Zimmerman, Hitchcock, and Crocker (3,4) exposed over 100 species to experimental concentrations ranging from 115 to 575,000 mg/m^3 (100 to 500,000 ppm). The plants were exposed to CO under bell jars or in Wardian cases, with apparently no regulation of concentration after introduction of the gas into the chamber. Exposure time ranged from 7 to 23 days. The fact that concentrations of 115 mg/m^3 (100 ppm) caused "practically" no growth retardation suggests that concentrations of CO needed to affect plant growth were considerably higher than those normally encountered in ambient air.

The experiments at Boyce Thompson Institute showed that plant species varied widely in their susceptibility to CO and in symptom expression. The most important detrimental responses were: epinasty (downward curl) and hyponasty (upward curl) of leaf stem; increased rate of aging of leaves and stimulation of abscission of leaves, flower buds, and fruits; overgrowth of lenticular tissue; retardation of stem growth; reduction of leaf size; initiation of adventitious roots from young stem or leaf tissue; and modification of the natural response to gravity, causing the roots to grow upward out of the soil.

Several researchers reported alterations of plant characteristics by exposure to CO. At a concentration of 11,500 mg/m^3 (10,000 ppm) "feminization" of plants occurred (5-7). Female sex expression is promoted in relation to male by early formation of pistillate flowers and an increase in the number of flowers. The effects on flower formation, leaf epinasty, abnormal stem growth, and adventitious root formation suggest substantial elevation in auxin content in CO treated plants. Dubrovina (8) reported that seeds pretreated with CO before planting produced plants with increased leaf size. Amoore (9) described a reduction in adenosine triphosphate production during a 4-hour exposure to 460,000 mg/m^3 (400,000 ppm) of CO plus an oxygen and nitrogen mixture.

The effects of CO on microorganisms are focused primarily on inhibition of nitrogen fixation. Nitrogen fixation by microorganisms is of great importance to the life of higher-type plants. Lind and Wilson (10) showed that fixation of free nitrogen by Azotobacter vinelandii, a free-living nitrogen-fixing bacterium, was inhibited when cultures were exposed to 2,300 mg/m^3 (2,000 ppm) CO for 35 hours. Uptake of combined forms of nitrogen such as ammonium nitrate, ammonium phosphate, sodium nitrate, and urea were unaffected by CO levels as high as 5,750 mg/m^3 (5,000 ppm) during the same exposure time. The same authors, using the same bacteria but employing microrespiration techniques, found some inhibition of combined nitrogen uptake at 6,900 mg/m^3 (6,000 ppm) for 4 hours (11).

Lind and Wilson (12) exposed red clover plants inoculated with Phizobium trifolli for 1 month to 0, 58, 115, 230, 345, 575, and 1,150 mg/m^3 (0, 50, 100, 200, 300, 500, and 1,000 ppm) of CO in separate treatments. At 0 and 58 mg/m^3 (0 and 50 ppm) CO, no inhibition of nitrogen fixation was detected, but a 20 percent reduction in total nitrogen production occurred at 115 mg/m^3 (100 ppm). At 575 mg/m^3 (500 ppm) inhibition of nitrogen fixation was essentially complete. By comparison, noninoculated plants supplied with nitrogen in the form of ammonium nitrate showed no effects of CO at concentrations of 1,150 mg/m^3 (1,000 ppm). Parallel experiments reported in the same paper showed similar results when rate of nitrogen fixation, rather than total nitrogen, was considered.

B. SUMMARY

Carbon monoxide has not been shown to produce detrimental effects on higher-type plant life at concentrations below 115 mg/m^3 (100 ppm) during exposures of 1 to 3 weeks. Nitrogen fixation by free-living bacteria was inhibited at exposures of 2,300 mg/m^3 (2,000 ppm) CO for 35 hours. Nitrogen fixation by efficient nitrogen-fixing bacteria in clover roots was also inhibited by 115 mg/m^3 (100 ppm) CO when exposed for 1 month.

Ambient CO levels rarely reach 115 mg/m^3 (100 ppm) even for very short periods of time. In view of this and the foregoing information concerning CO effects, a significant impact on vegetation and associated microorganisms seems improbable.

It should be pointed out that no information is available on CO concentrations in soils. Most higher plants grow with their roots in the soil, and nitrogen-fixing organisms as soil dwellers would be vulnerable to soil-borne CO. Hundreds of species of both flora and fauna, whose activities are important to soil development and to plant growth, may also be affected.

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CHAPTER 7.

TOXICOLOGICAL APPRAISAL OF CARBON MONOXIDE

A. INTRODUCTION

There is extensive documentation of the fact that high concentrations of carbon monoxide (CO) can cause many physiological and pathological changes and ultimately death. The effects of exposure to levels of CO of less than 115 mg/m^3 (100 ppm) are not so well documented. The purpose of this chapter is to evaluate the data on experimental exposure of animals and humans to CO, emphasizing both the acute and long-term effects of low CO concentrations. A recent (1969) review (1) provides additional information on most of the studies discussed in this chapter, particularly with regard to areas for future research.

The principal toxic properties of CO are based on its reactions with hemoproteins. The most important of these reactions is the reversible combination of CO with hemoglobin (Hb) to form carboxyhemoglobin (COHb). In addition to varying exposures to exogenous CO, the body is steadily exposed to a small amount of endogenous CO formed as a by-product in the course of heme catabolism; in normal humans, this amounts to about 0.4 milliliter of CO per hour. The presence of this relatively small amount of CO results in a "normal" or "background" level of COHb in the bloodstream of about 0.5 percent.

Oxygen and CO react with hemoglobin in a similar manner, and their transport depends on their reaction with the iron atom of the heme prosthetic group. The affinity of hemoglobin for CO is more than 200 times greater than that for oxygen.

Heme is an iron complex of protoporphyrin. The iron, in the ferrous form, combines reversibly with ligands in a ratio of 1:1. There are four heme units in the hemoglobin molecule and, hence, four molecules of oxygen or CO may be utilized in the formation of saturated oxyhemoglobin (O_2Hb) or carboxyhemoglobin (COHb). Hemoglobin may also be present in a reduced form, which is the predominant source of the darker color of venous blood. When the iron is in the oxidized form, the molecule becomes methemoglobin, which is inactive in the transport of oxygen or CO.

The dissociation curves of O_2Hb and COHb are sigmoid in shape. The sigmoid character of the dissociation curves implies that the affinity of the binding sites changes as a result of the presence of the ligand on the other sites; i.e., there are interactions between the various binding sites. These are commonly called the heme-heme interactions or allosteric effects. Since one hemoglobin molecule contains four heme units, the binding of oxygen or CO to these units may be associated with conformational changes that reflect these interactions in the protein molecule.

Carbon monoxide is potentially capable of reacting with other hemoproteins in vivo. In vitro it will combine with myoglobin (Mb) to form carboxymyoglobin (COMb) and may also interfere with certain enzyme systems. The biologic significance of these reactions will be discussed in Section G of this chapter.

B. THEORETICAL CONSIDERATIONS

When air containing a certain concentration of CO is inhaled for several hours, a state of equilibrium with respect to this gas is reached in which the partial pressure of CO (P_{CO}) in the pulmonary capillary blood is virtually equal to that in the alveolar and ambient air. The equilibrium of the reaction:

$$CO + Hb \rightleftharpoons COHb$$

depends on the partial pressure of CO (P_{CO}) and of oxygen (P_{O_2}) because the two gases compete for the same reactive sites on the hemoglobin molecule. The relationship is described by the Haldane equation:

$$\frac{[COHb]}{[O_2Hb]} = M \times \frac{P_{CO}}{P_{O_2}}$$

where [COHb] and [O_2Hb] are the concentrations of COHb and O_2Hb (usually expressed as percent saturation), and M is the relative affinity constant. At physiologic pH and temperature, the value of M is about 210, although values of up to 245 have been reported (2). This means that the affinity of hemoglobin for CO is about 210 times that for oxygen, or that equal amounts of COHb and O_2Hb exist in equilibrium with gas mixtures containing 210 oxygen molecules for every CO molecule.

Although a number of theories and models have been proposed to explain the sigmoid shape of the oxygen dissociation curve (a plot of the partial pressure of oxygen against the percentage of hemoglobin present at O_2Hb), none has adequately explained all of the various features and kinetics of the reaction of hemoglobin with ligands. At present, the Adair (3) model seems the most acceptable, although it is likely to be oversimplified since some aspects of the equilibrium and kinetics of hemoglobin cannot be accommodated within its framework.

Consideration of the toxicity of CO must include not only the displacement of oxygen from hemoglobin in arterial blood, but also the interference with oxygen release at the tissue level. The latter effect can be understood by a study of the O_2Hb dissociation curve as described by Roughton and Darling (4) (Figure 7-1). The presence of COHb causes a shift of the O_2Hb dissociation curve to the left for the remaining hemoglobin (not bound to

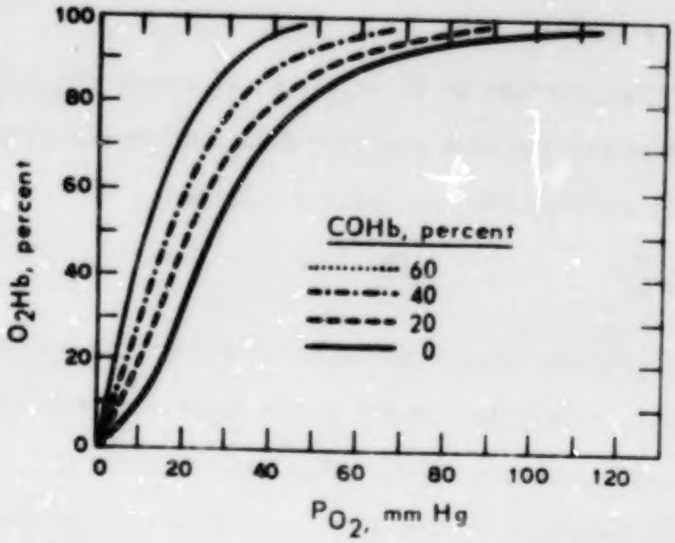

Figure 7-1. Oxyhemoglobin (O_2Hb) dissociation curves of human blood containing varying amounts of carboxyhemoglobin (COHb), calculated from observed oxygen dissociation curve of carbon monoxide-free blood (pH = 7.4, T = 37 °C, P_{CO_2} = 40 mm Hg) (4).

CO), which implies that for a given oxygen saturation there is a lower partial pressure of oxygen. The shift of the O_2Hb dissociation curve is best understood if the most accessible binding sites are considered to be those that first pick up and discharge CO or oxygen. Essentially, the bottom part of the S-shaped hemoglobin dissociation curve is inactivated by CO; therefore, only the top part reacts with oxygen. This top part, then, is reexpanded to fit between vertical and horizontal axes with altered scales for O_2Hb and P_{O_2}, respectively.

Since the increased affinity of hemoglobin for CO implies that some of the accessible sites are occupied by CO while the hemoglobin molecule circulates through the body several times, it would also mean that some of the sites that would convey labile oxygen are actually conveying nonlabile CO. The P_{O_2} of mixed venous blood (40 mm Hg) occurs at a steep part of the curve, and the effect of a shift to the left on release of oxygen at the tissue level may be considerable.

At rest, there is a close correlation between the P_{O_2} of mixed venous blood and the P_{O_2} of the tissues; hence, a lowering of the mixed venous P_{O_2} following CO inhalation reflects a similar decrease in the tissue P_{O_2}. Klausen et al. (5), using eight healthy male students as subjects, have estimated a 15 to 20 percent lowering of the tissue P_{O_2} at rest in response to the presence of an average of 15 percent COHb. Measurements on animals are in good agreement with this estimate (6).

The effect of CO on the O_2Hb dissociation curve has been demonstrated experimentally *in vitro* with solutions of human hemoglobin (2). The leftward shift of the oxygen dissociation curve has also been demonstrated by Lilienthal et al. (7) *in vivo*; the data given in their paper have been recalculated (Table 7-1) and are shown graphically in Figure 7-2. More recently, Mulhausen et al. (8) have shown that the average P_{O_2} corresponding to 50 percent O_2Hb saturation dropped from 26.7 to 23.2 mm Hg in eight subjects who were intermittently exposed to CO and who had an average of 15 percent COHb at the end of the 7-day exposure period.

In these theoretical considerations, the impairment of oxygen delivery to the tissues is only implied from the O_2Hb dissociation curve. Recently, however, Baumberger et al. (9) created an experimental model by which to study the oxygen delivery rate (ODR) of human blood *in vitro*. They found that the ODR increased with a decrease in percent saturation of hemoglobin and that there were significant differences in the ODR between individuals. Whether the ODR responds to small amounts of COHb at a fixed saturation of hemoglobin *in vivo* remains to be determined.

C. MEASUREMENT OF CARBOXYHEMOGLOBIN IN BLOOD

Many methods exist for the determination of blood COHb. Three categories of analytical methods are available: nondestructive, destructive,

Table 7-1. BLOOD AND GAS STUDIES (AVERAGES OF TWO MEASUREMENTS TAKEN 30 MINUTES APART) AFTER ADMINISTRATION OF CARBON MONOXIDE AND AIR UNTIL ATTAINMENT OF CARBOXYHEMOGLOBIN EQUILIBRIUM (7)

Subject	No. on Fig. 8–2	PaO_2, mm Hg	PaO_2 + MpCO,[a-c] mm Hg	Arterial O_2Hb, % sat.	Arterial COHb, % sat.	Arterial O_2Hb + COHb, % sat.	$100 \times \frac{O_2Hb}{COHb + O_2Hb + Hb}$	$100 \times \frac{O_2Hb + COHb}{COHb + O_2Hb + Hb}$
1	1	57.5	62.7	88.9	7.5	89.8	83.4	90.4
(Light smoker)	2	56.0	60.9	88.1	7.3	88.9	82.9	89.7
2	3	40.0	48.7	80.7	15.0	83.5	72.3	85.2
(Heavy smoker)	4	67.5	89.1	97.1	23.7	97.8	81.0	96.2
3	5	63.5	74.3	96.2	14.1	96.7	83.3	97.6
(Nonsmoker)	6	54.0	59.7	89.1	8.6	90.0	82.7	90.8

[a] PaO_2 + MpCO = adjusted O_2 tension.

[b] $MpCO = P_{O_2} \times \frac{[CO]}{[O_2]}$.

[c] $M = 210 = \frac{P_{O_2} \times [COHb]}{P_{O_2} \times [O_2Hb]}$.

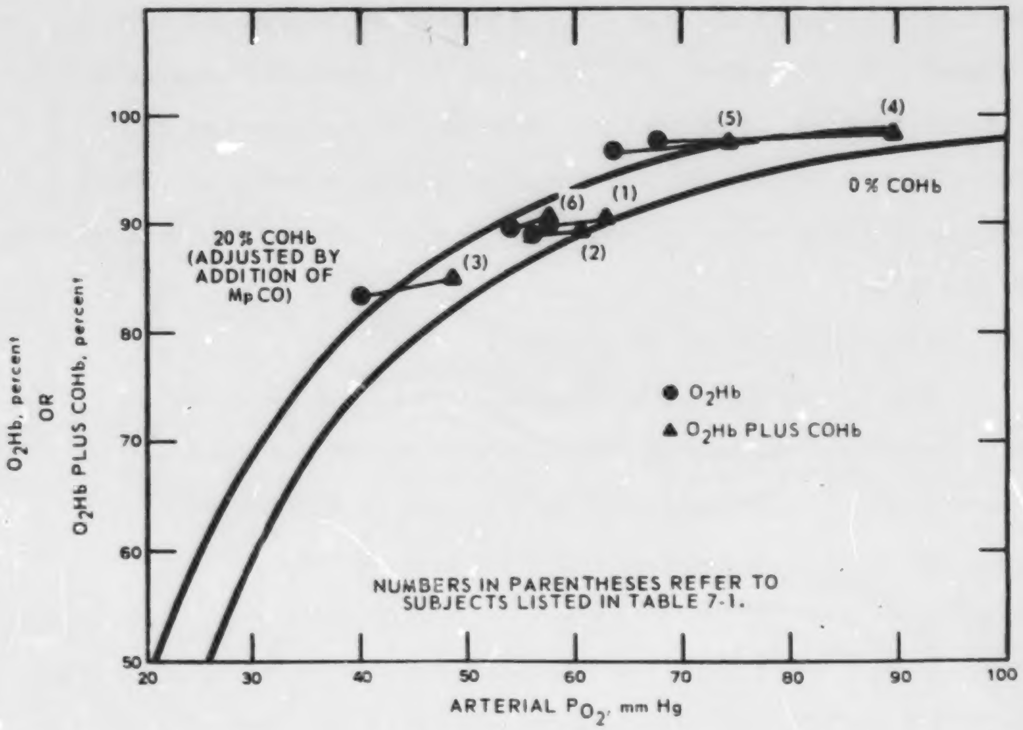

Figure 7-2. Effect of carbon monoxide administration on arterial oxygen tension (P_{O_2}), compared with oxygen dissociation curves in Figure 7-1, based on data in Table 7-1.

and equilibrium. Analyses must be done at least in duplicate (10,11) and preferably by two different techniques, with disparities in results accounted for and resolved. The methods selected for use must be evaluated with respect to general accuracy, precision, volume of blood required, and accuracy at low COHb levels. In addition, the methods must be evaluated with respect to the needs and resources of individual laboratories.

1. Nondestructive Methods

Nondestructive methods, which are mainly spectrophotometric, can be divided into ratio and extinction methods. Difficulties arise when the spectral densities of methemoglobin, pathologic or variant hemoglobin types, and hemoglobin breakdown products are superimposed on the O_2Hb and COHb spectrograms. Several authors (10,12,13), who have conducted comparative analyses using various nondestructive techniques have argued that many spectrophotometric methods may give deceptive results at levels of COHb below 10 percent. The most recent methods (14), however, appear to be more reliable at low levels.

a. Ratio Methods

Since the absorption characteristics of COHb and O_2Hb are similar, the ratio of COHb to O_2Hb is calculated by means of a ratio derived from measuring the extinction coefficients at different wave lengths. The original method used by Huefner (15) employed two wave lengths and was later refined by Heilmeyer (15), Klendshoy (16), Schwerd (17), and Amenta (18), who introduced additional wave lengths. All these methods require a calibration curve whose terminal points are a pure COHb solution and a pure O_2Hb solution, respectively. For the terminal point to reflect 100 percent COHb reliably, the CO partial pressure in the plasma must be higher than 700 mm Hg in order to saturate the blood to a level of 100 percent COHb. Only pure CO can be used; also, it should be noted that the kinetics Hb + CO = COHb are relatively slow. When substances are added to the saturated COHb solution for measuring purposes, these lower the 100 percent value and distort the calibration curve (18,19). Furthermore, reduced Hb in the venous blood can frequently influence the results through interference at 416 and 410 nm.

In the spectrophotometric methods used by Amenta (18), diluted ammonium hydroxide is added to the blood samples. The absorbances are determined at 575, 560, and 498 nanometers (nm). The ratio obtained,

$$R = \frac{A_{575} - A_{560}}{A_{498}}$$

is compared with the ratios obtained with standard solutions of O_2Hb and COHb. Percent COHb is calculated from the equation,

$$\% \text{ COHb} = 100 \times \frac{R_{O_2} - R_x}{R_{O_2} - R_{CO}}$$

where R_{O_2}, R_{CO}, and R_x are the ratios obtained, respectively, from 100 percent O_2Hb, 100 percent COHb, and the unknown COHb solution. The relationship between R_{CO} and COHb concentration is linear. Because at 498 nm the extinction coefficients of COHb and O_2Hb are the same, the absorbance at this wavelength can also be used to determine the total hemoglobin.

Tuddenham and Hitchcock undertook to evaluate this method, but found it somewhat unsatisfactory because of the inconsistent shift, induced by the varying concentrations of COHb, particularly at low levels, that prevented the construction of an acceptable calibration curve (19). The reproducibility of the isosbestic point for the determination of hemoglobin concentration, however, appeared to be satisfactory, with an accuracy to ± 0.39 percent hemoglobin.

Another spectrophotometric method is that of Commins and Lawther (20). In this method, the comparison of the absorption of COHb to that of 100 percent O_2Hb and 100 percent COHb is unsatisfactory for the following reason: the method of preparing standard solutions of 100 percent COHb and 100 percent O_2Hb involves bubbling CO or O_2 into the solutions. This produces an excess of dissolved gases; hence, when solutions containing less than 100 percent COHb were prepared, they were inaccurate. To overcome the above difficulties, mixed venous blood samples have been used that are equilibrated in separatory funnels with either CO (as described by Amenta, (18)) or air. By mixing calculated proportions of the two solutions, an acceptable calibration curve has been prepared. From the calibration curve, it appears that the method as described is sensitive enough to detect a minimum of 2 percent COHb. When mixed venous blood from heavy smokers and nonsmokers was assayed for COHb, small amounts of unsaturated hemoglobin in the sample caused substantial interference between the wavelengths of 416 and 410 nm. When O_2 was bubbled through the nonsmoker's blood sample, the interference disappeared, showing that the hemoglobin had become saturated. Interference caused by the saturated hemoglobin corresponded to about 10 percent COHb at 420 nm and about 20 percent at 439 nm.

In a critical discussion of the technique of Commins and Lawther, Buchwald (21) has reported slight modifications by which many of these difficulties seem to have been corrected. Small et al. (14) have most recently reported another spectrophotometric technique that is self-calibrating and does not require preparation of 100 percent COHb and O_2Hb. Critical evaluations by other laboratories have not yet been published, but the technique appears to be accurate at low levels, to be reproducible, and to use small samples.

b. Spectrophotometric Extinction Measurements of Isolated COHb

The methods developed by Wolff (22), Harper (23), Fretwurst (24), and Fuehr (25), which are widely used in Europe, are based on the fact that O_2Hb precipitates whereas COHb is more stable and remains in solution when hemalized blood is heated to a temperature of 55°C within a specified period and at a prescribed pH. Following this reaction, selective spectrophotometric measurements can be made of the COHb content. Major errors can be caused, however, by a deviation as small as 0.01 from the pH of the sodium acetate-acetic acid buffer (5.04), fluctuations in the temperature of the water bath (55°C), and variations in the heating period (26).

2. Destructive Methods

The destructive methods involve, for the most part, the liberation of blood gases with either total destruction of the hemoglobin or its transformation into a compound without any affinity for CO. The gases freed from the blood are then analyzed by various methods, and the CO present in them is assayed. The disadvantages of these methods are: 1) larger amounts of blood are required than for spectrophotometric methods; 2) separate determinations of hemoglobin concentrations must be made; and 3) the methods are fairly tedious. The released CO may be measured utilizing: 1) detector tubes; 2) the reaction of CO with palladium chloride; 3) manometric and volumetric methods; 4) infrared spectrophotometry; and 5) gas-phase chromatography.

a. Carbon Monoxide Detector Tubes

Carbon monoxide detector tubes have been used to assay CO in gases extracted from blood. Views on the reliability of this method are varied, although the method reportedly has an accuracy of 2 to 20 percent that of the manometric method (27). The detector-tube method gives only an estimate of the CO content of blood and is not suitable for accurate determinations. (Technical data on carbon monoxide detector tubes can be found in Chapter 4, Section C.2.e of this report.)

b. Reduction Methods

The Gettler-Freimuth method (28), based on use of a test spot, does not appear to be useful for determination of COHb levels below 10 percent.

The turbidometric method of Kohn, Abrest, and Gramer (26) and the Conway method (29) are accurate at lower levels.

A microdiffusion apparatus is used for the Conway method. The blood gases are liberated, and the CO released reduces the palladium chloride to metallic palladium. The excess palladium chloride is usually assayed by volumetric analysis or colorimetry (30). The method is said to be sensitive to 1 percent COHb (standard deviation (SD) of approximately ±0.03 ml/100 ml). The disadvantage is that the method is tedious and requires a skilled chemist to perform it.

c. Manometric and Volumetric Methods

Manometric methods include the techniques of Van Slyke (31) (SD ± 0.05 ml/100 ml) and Horvath and Roughton (32) (SD ± 0.03 ml/100 ml). The volumetric methods that have been successfully used are the syringe capillary method of Scholander and Roughton (33) (SD + 0.03 to - 0.05) and the Van Slyke syringe technique of Roughton and Root (34) (SD ± 0.007 ml/100 ml). These methods are accurate and are considered adequate, although they are time-consuming, are technically difficult, and require large volumes of blood. There is some doubt, however, as to the sensitivity of the methods to COHb at levels below 5 percent.

d. Spectrophotometric Determination of Released CO by NDIR (Nondispersive Infrared) Method

This method provides highly accurate results, but requires costly equipment. Methods based on this technique have been published by Rossmann (35) and later by Coburn et al. (36) (SD ± 0.006 ml/100 ml in the range of 0.1 to 1.0 ml/100 ml) and by Schuette (37). Care must be taken to maintain the correct pH range and to prevent warming the blood prior to extracting the CO; otherwise, inaccurate results are obtained. A small amount of mercury is required to prevent CO formation from hemoglobin breakdown. An advantage of this method is that measurement of CO by the NDIR method is virtually specific (for a discussion on interferences, see Chapter 4, Section C.1.b on measurement of atmospheric CO by NDIR) and is considerably more sensitive than the other methods previously described.

e. Gas-phase Chromatography

Hackney et al. (38) have successfully used gas-phase chromatography in which the CO is released from blood in the Van Slyke apparatus, diluted, and then flushed through a gas chromatograph. The characteristics of the chromatography system are described in detail in the original paper. The sensitivity of the method is about 20 parts per million ± 1 percent with a 25-cubic-centimeter gas-sample size. Substantial refinement of this method is afforded by a reduction of CO to CH_4 and its measurement by a flame ionization detector (39), or by direct measurement of CO with a helium ionization detector capable of determining CO in the parts-per-billion range.

f. Determination of Total Hemoglobin

The destructive methods described provide data for only the concentration of CO in blood; to obtain the percent COHb present, separate determinations of hemoglobin must be made. The determination of Hb concentration requires the same meticulous care needed for CO measurement (40). Spectrophotometric methods can be used. When the cyanide method is used, care must be taken to ensure that when COHb is present the formation of cyanide is slowed down. Therefore, the reading must not be taken before some 30 to 50 minutes have elapsed, depending on the expected COHb content.

3. Equilibrium Methods - Analysis of Expired Air

The analysis of expired air cannot be categorized as destructive or nondestructive. Its success depends on the consideration that the lung, during breath-holding, is thought to be analogous to a closed vessel in which blood COHb equilibrates with the lung gas. Sjostrand (41), Jones et al. (42), and, more recently, Ringold et al. (43) have shown that COHb may be estimated from expired air after breath-holding for 20 seconds. The subject is asked to exhale deeply, to take a deep inspiration, and hold his breath for 20 seconds; at the end of that time, the subject is asked to expire through a side-arm tube. The first 150 to 250 milliliters of gas is allowed to escape, and the remaining gas expired from the lung is collected into a polyvinyl bag with a simple push-pull valve. Several studies have produced graphs correlating expired air CO with blood COHb.

The method as published appears to be suitable for studying the relationship of COHb to occupational and ambient air pollution exposures where large populations need to be studied. Recent studies have shown, however, that the CO content of expired air in smokers does not always correlate well with blood COHb. Thus, further studies are required to demonstrate the validity of this method for all subjects.

4. Discussion

The most accurate methods for determination of COHb are generally those that liberate and measure the CO bound to hemoglobin. The CO should be determined by NDIR or gas chromatography. The hemoglobin must be determined separately with the same accuracy.

D. UPTAKE OF CARBON MONOXIDE BY HUMANS

Two basically different methods can be used to predict carboxyhemoglobin levels resulting from a known exposure to CO. The first of these consists of using empirically derived prediction formulas based on controlled exposure experiments. These relationships have been studied since carbon monoxide was recognized as a toxic substance, but the first person in the United States to explore systematically the kinetics of CO exposure was Forbes (44). At about the same time, Pace (45) and Lilienthal (7) and their co-workers published similar observations. The formulas derived from these data describe carboxyhemoglobin formation as a linear function of exposure time, and are accurate only for about 4 hours of exposure.

Forbes made approximately 100 observations on seven presumably healthy male adults exposed to 115 to 23,000 mg/m^3 (100 to 20,000 ppm) CO for periods of up to 5 hours at the lower levels of CO (44). Not all of the subjects were exposed to each concentration for each exposure time. Four grades of activity were used: 1) rest (subject lying upon a bed); 2) light activity (walking about the chamber, taking blood samples, and reading instruments); 3) light work (riding a bicycle ergometer at 50 watts, or 2220 foot-pounds per minute, which is activity equal to walking on the level); and 4) heavy work (riding a bicycle ergometer at 100 watts, or 4440 foot-pounds per minute, which is activity equal to a slow jog trot). Blood COHb was determined by the Scholander and Roughton (46) method. (Reservations pertaining to this method of analysis have been discussed in Section C of this chapter.) Although no information concerning the smoking habits of the subjects is given in Forbes' paper, the stated preexposure COHb values of 0 to 5 percent suggest that some of the subjects were probably smokers.

Nearly half of the observations were made on subjects engaging in light activity. Average results for the whole range of activities and inspired CO (0 to 23,000 mg/m^3) are given in Figure 7-3. Figure 7-3 also indicates the percentage COHb increase that would be expected for the various concentrations of CO at equilibrium. Although no individual data are given in the figure, it should be noted that out of 41 observations, 18 were off the curves by only 1 percent COHb or less, 9 were off by 2 percent, 9 by 3 percent, 3 by 4 percent, and 2 by 5 percent. These individual variations are believed to be due to variations in the ratio of tidal volume to the dead space of the lung and also to the diffusion constant of the lung (DL_{CO}).

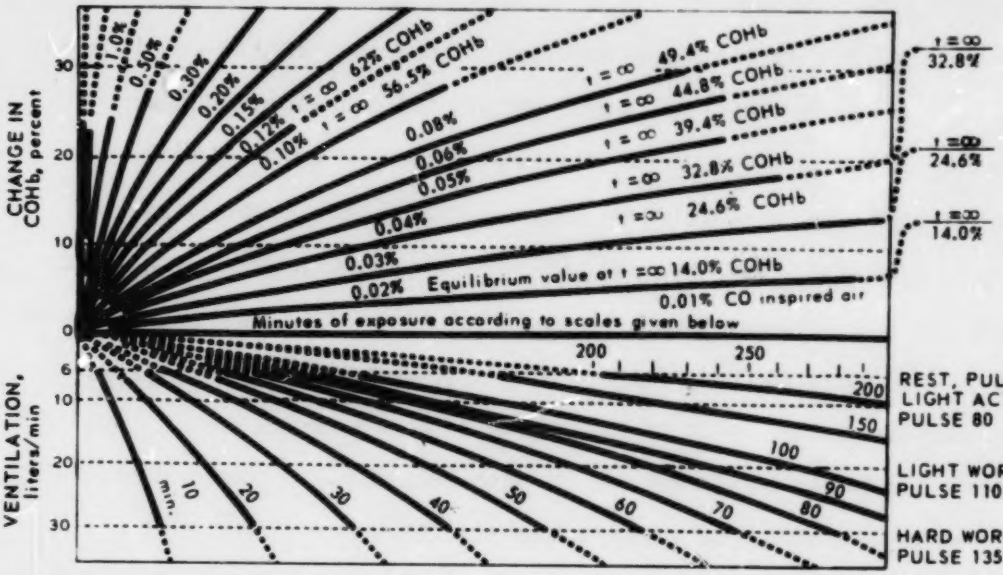

Figure 7-3. Uptake of CO at various concentrations and rates of ventilation (44).

The data in Figure 7-3 show that the uptake of CO by the blood increases with: 1) the concentration of CO; 2) the length of exposure; and 3) the ventilation rate. The rate of uptake, as estimated by the linearity of COHb with time, appears to be constant up to values of approximately one-third of the equilibrium level of COHb for a given concentration. For example, it is demonstrated in Figure 7-3 that exposure to 575 mg/m^3 (500 ppm, or 0.05 percent) CO for 10, 20, 40, and 80 minutes during light work results in respective increases of COHb of approximately 4, 8, 12, and 22 percent.

In Forbes' studies, when CO was administered in 98 percent oxygen instead of in air, the rate of CO uptake decreased. This effect was more pronounced in experiments in which subjects had undergone hard work rather than remaining at rest. For reasons unknown, some subjects were found to hyperventilate in response to the 98 percent oxygen, and their apparent rate of uptake under these conditions was not the same as when the CO was in air. When a correction was made to take into account the increased ventilation, uptake at rest was reduced 23 percent and during hard work 38 percent. Exposure of four subjects to 3450 to 4600 mg/m^3 (3000 to 4000 ppm) CO for 6 minutes at an atmospheric pressure of 410 mm Hg, simulating an altitude of 4877 m (16,000 ft), produced no alteration in the rate of uptake of CO when a correction was made for hyperventilation due to anoxia (44). These experiments will be discussed more fully in Section H of this chapter.

One study made of exposure of humans to low concentrations of CO (less than 115 mg/m^3, or 100 ppm) was reported recently by Smith (47). The average data for the seven nonsmokers involved in the study are shown in Figure 7-4. In these subjects, exposure to 35 mg/m^3 of CO produced a blood level of about 5 percent COHb at equilibrium.

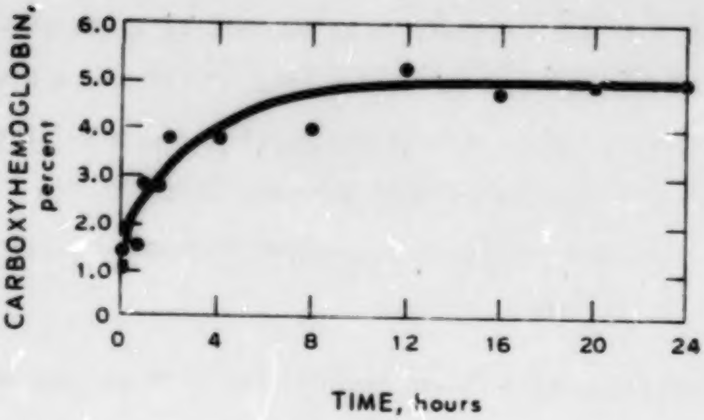

Figure 7-4. Average values of percent carboxyhemoglobin in seven nonsmokers exposed to 35 mg/m^3 (30 ppm) carbon monoxide (47).

A relatively simple formula for estimating the increase in the equilibrium value of COHb above background after continuous exposure to CO concentrations of less than 115 mg/m^3 (100 ppm) has recently been included in a review (48) of the effects of CO:

$$\% \text{ COHb} = 0.16 \times \text{ppm CO}$$

Thus after an exposure to 35 mg/m^3 (30 ppm) CO, the predicted equilibrium value of COHb would be 4.8 percent, which is identical to Smith's results.

Experimental data are available for estimating the blood COHb levels anticipated after exposures to CO for periods of time less than would be necessary to attain equilibrium. Peterson and Stewart (49) studied young human volunteers exposed to a range of CO for periods of 30 minutes to 24 hours. Blood COHb was measured periodically during the experiment by both a direct determination in a CO-Oximeter* and by measuring CO, liberated from the COHb, by means of a gas chromatograph equipped with a helium ionization detector. The following relationship was derived to describe the absorption of CO by these subjects:

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*Instrumentation Laboratories, Waltham, Massachusetts.

$$\% \text{ COHb} = \frac{(\text{CO}^{0.858}\ t^{0.63})}{197}$$

where CO is measured in ppm and t is the duration of exposure in minutes. Hanks (50) has also conducted carefully controlled exposure studies and expressed his data with the formula:

$$\% \text{ COHb} = \frac{(8.5\ \text{CO})\ 1 - e^{-0.1735t}}{58}$$

where CO is measured in ppm and t is the duration of exposure in hours.

These formulas predict COHb levels that are statistically different from each other over most of the usual exposure range. For exposures longer than 8 hours, the formula of Peterson and Stewart predicts COHb levels much higher than levels derived by Hanks' formula or those reported by Smith.

Coburn, Forster, and Kane published a detailed theoretical analysis of the physiology and variables that determine blood carboxyhemoglobin values in man (51). Some of these are schematically depicted in Figure 7-5.

The basic relationship they describe is:

$$\frac{A\ [\text{COHb}]_t - V_{co}B - P_{I_{co}}}{A\ [\text{COHb}]_0 - V_{co}B - P_{I_{co}}} = e^{(-tA/V_bB)} = e^k$$

where:

$[\text{COHb}]_t$ = carboxyhemoglobin concentration at
t = minutes exposure.
Sample calculation:
2.5% COHb = (0.025) (1.34) (0.15) = 0.005 ml CO/ml blood

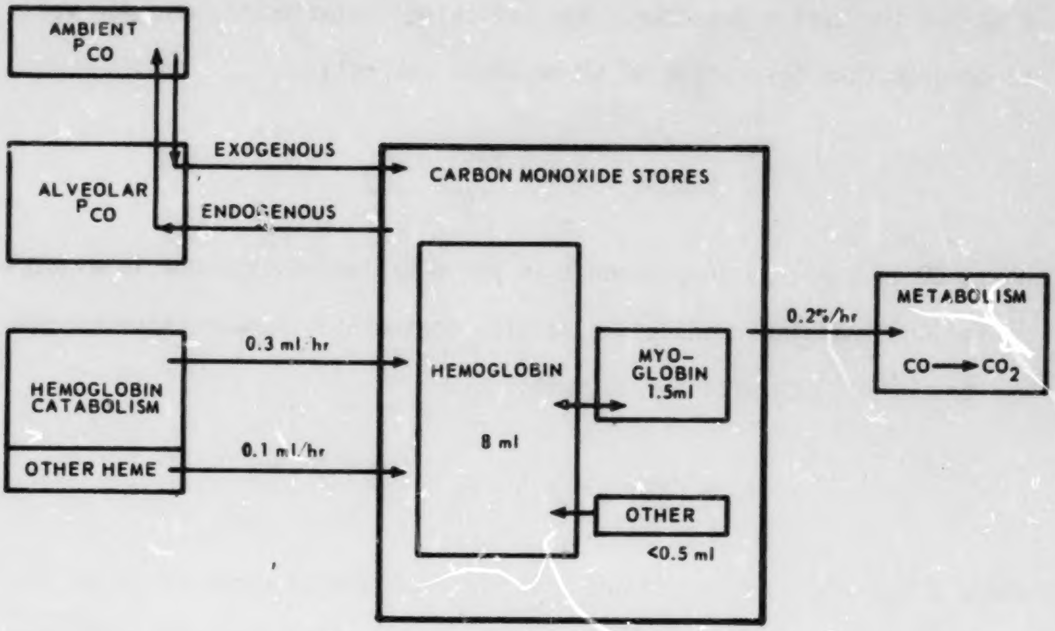
AMBIENT
P_{CO}
ALVEOLAR
P_{CO}
EXOGENOUS
ENDOGENOUS
CARBON MONOXIDE STORES
HEMOGLOBIN CATABOLISM
OTHER HEME
0.3 ml/hr
0.1 ml/hr
HEMOGLOBIN
8 ml
MYO-GLOBIN
1.5ml
OTHER
<0.5 ml
0.2%/hr
METABOLISM
$CO \rightarrow CO_2$

Figure 7–5. Diagramatic summary of current concepts regarding variables that influence body CO stores (52).

$[COHb]_o$ = carboxyhemoglobin concentration, in ml CO/ml blood, at t = o

Sample calculation:
1 gram of Hb combines stoichiometrically with 1.34 ml of CO or O_2. Assuming 15 g% Hb:
0.5% COHb = (0.005) (1.34) (0.15) = 0.001 CO/ml blood

$[O_2Hb]$ = oxyhemoglobin in ml O_2/ml blood.
Assuming 100% saturation of arterial blood:
$[O_2Hb] = (1.34)\ (0.15) = 0.201$ ml O_2/ml blood.

$$A = \frac{\bar{P}_{c_{O_2}}}{M[O_2Hb]}$$

where:

$\bar{P}_{c_{O_2}}$ = pulmonary capillary O_2 tension at sea level ($\overset{\sim}{=}$ 100 mm Hg).

M = relative affinity of Hb for CO and O_2 ($\overset{\sim}{=}$ 218).

$$B = \frac{1}{D_L} + \frac{P_L}{V_A}$$

where:

D_L = pulmonary diffusing capacity for CO $\cong$ 30 ml/min-mm Hg.

P_L = sum of partial pressures of alveolar gases excluding water vapor (47 mm Hg at 37° C).

$P_L \cong 760 - 47 = 713.$

V_A = alveolar ventilation ($\cong$ 4200 ml/min at rest).

V_b = blood volume ($\cong$ 5500 ml for 70-kilogram man).

$P_{I_{co}}$ = partial pressure of CO in inspired air.

$$\text{ppm CO} = \frac{P_{I_{co}} \times 10^6}{\text{Barometric pressure}}$$

$\dot{V}_{co}$ = rate of endogenous CO production. This is related to heme metabolism, which can vary considerably, because it is a function of red blood cell life span. Any factor reducing RBC survival elevates V_{co}. A reasonable, average value for healthy adults = 0.007 ml/min.

The most useful rearrangements of the basic relationship are:

$$P_{I_{co}} = \frac{e^k \left[A[\text{COHb}]_o - \dot{V}_{co}B\right] + \dot{V}_{co}B - A[\text{COHb}]_t}{e^k - 1} \tag{1}$$

Equation 1 permits calculation of the exposure level needed to produce a given change in COHb over a given time:

$$[\text{COHb}]_t = \frac{e^k \left[A[\text{COHb}]_o - \dot{V}_{co}B - P_{I_{co}}\right] + \dot{V}_{co}B + P_{I_{co}}}{A} \tag{2}$$

so that COHb resulting from a given exposure level for a given duration of exposure can be calculated (Equation 2).

Careful comparison of these relationships with available human exposure data confirms the general validity of using a theoretical model to solve the complicated problem of predicting COHb levels under a variety of experimental and clinical conditions.

Figure 7-6 shows a comparison of carboxyhemoglobin levels predicted by three empirical formulas and the theoretical model. For the first few hours of exposure, the formulas of Hanks and Forbes agree very well with the model. Stewart's formula is higher than the others from the beginning, and this difference is accentuated with time. Forbes' linear relationship is only applicable to about the first 4 hours of exposure. In order to examine the behavior of these formulas with long exposure times, the curves in Figure 7-7 were calculated. The inapplicability of both Forbes' and Stewart's formulas to long exposure times is dramatized. Data from the study of Peterson and Stewart (49), however, agree well with the formula of Coburn et al.(50). Values derived with Hanks' formula are virtually indistinguishable from those given by the theoretical model for the first 10 hours, and both come into equilibrium at about the same time, with

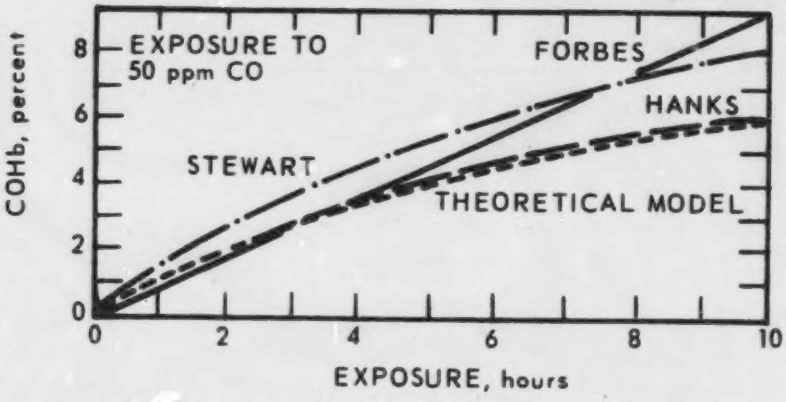

Figure 7-6. Comparison of carboxyhemoglobin levels predicted by three empirical formulas and a theoretical model.

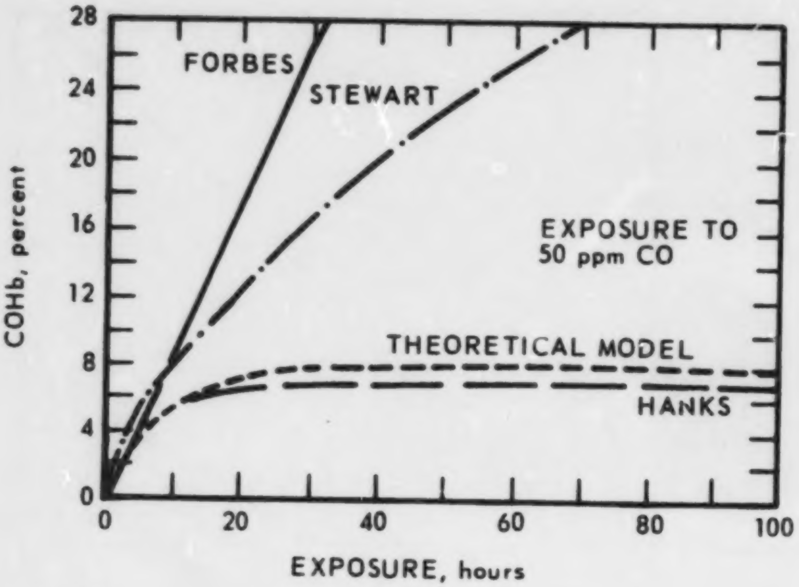

Figure 7-7. Comparison of carboxyhemoglobin levels predicted by three empirical formulas and a theoretical model over long exposure times.

relatively little separation between the two asymptotes. Figure 7-8 shows the comparison of equilibrium values for arbitrarily chosen exposures calculated from the formula of the California State Board of Public Health (48) and from the theoretical model. The points lie quite close to the 45-degree line of identity.

It seems, therefore, that values calculated by the mathematical formula agree closely with available data when those data are properly interpreted. In addition, of course, the theoretical model allows computer simulation of CO exposure kinetics with a large number of input parameters. Great care, however, must be exercised in choosing appropriate and internally consistent values for these parameters and in interpreting the results of modeling in a context that is physiologically reasonable.

The formula of Coburn et al. becomes much more versatile and general if the alveolar air equation (53) and certain empirical relationships

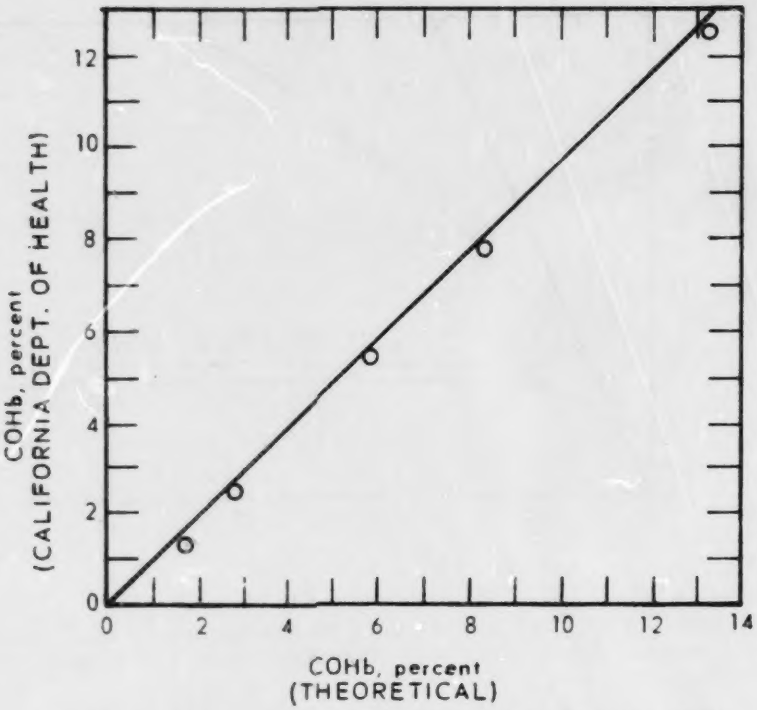

Figure 7-8. Comparison of equilibrium values of carboxyhemoglobin for arbitrarily chosen exposure durations, calculated by the California State Department of Health's formula and the theoretical model.

between altitude and physiologic variables (54) are included.

The alveolar air equation is:

$$P_{A_{O_2}} = F_{I_{O_2}} (BP-47) - P_{A_{CO_2}} \left[F_{I_{O_2}} + 1 - \frac{F_{I_{O_2}}}{R}\right]$$

where:

$P_{A_{O_2}}$ = Alveolar oxygen tension.

$F_{I_{O_2}}$ = Fraction of oxygen in inspired air.

BP = Barometric pressure.

$P_{A_{CO_2}}$ = Alveolar CO_2 tension.

R = Respiratory exchange ratio, $\dot{V}_{CO_2}/\dot{V}_{O_2}$.

Assuming a negligible alveolar-to-arterial O_2 gradient, pulmonary capillary O_2 tension approximately equals alveolar O_2 tension. The alveolar air equation, therefore, can be used in the definition of factor A in the Coburn formula.

Simulation of the effects of altitude can be accomplished with the following empirical relationships:

$$P = 760\ e^{-\frac{a}{7924.826}}$$

where:

P = atmospheric pressure, in mm Hg.

a = altitude above sea level, in meters.

The calculated atmospheric pressure at altitude can thus be substituted for actual measured pressure in the alveolar air equation and in the conversion from ppm CO to $P_{I_{CO}}$. It is important to remember that the conversion from mass to volume units in aerometry also involves atmospheric pressure. Thus, the details of instrument calibration must be known before one can decide whether or not it is appropriate to include an atmospheric pressure correction factor in calculating $P_{I_{CO}}$ from mass units. The percentage of reduced hemoglobin formed as a result of exposure to altitude.

$$\%\ RHb = 2.76\ e^{\frac{a}{2133.607}}$$

This must be added to the % RHb present in a given individual at sea level and must also be taken into consideration when factor A in the Coburn equation is calculated.

Permutt and Farhi have emphasized the importance of considering the effect of CO exposure on tissue oxygenation (55); this effect can, as well, be calculated from known physiologic variables. Thus, reliable mathematical modeling of the effect of CO exposure on tissue oxygenation is possible.

E. EFFECT OF CARBON MONOXIDE UPON THE CENTRAL NERVOUS SYSTEM

Energy required for maintaining the structure and function of the brain is primarily supplied by processes that depend upon oxygen. Although the brain makes up only 2 percent of body weight, it accounts for about 20 percent of the entire body's oxygen requirement. Consequently, central nervous system function is particularly susceptible to hypoxia. Depending upon the severity and the duration of hypoxia, symptoms of hypoxia can range from functional disturbances to deep unconsciousness and can be temporary or permanent.

Individuals who have circulatory insufficiency, especially cerebral circulatory insufficiency, are particularly endangered by exposure to CO. In these cases, serious impairment of cerebral oxygenation may occur even upon slight exposure to CO. It is therefore clear why individuals with impaired cerebral circulation (e.g., arterial sclerosis), the elderly and the sick, in particular, exhibit increased sensitivity to CO, with the danger of delayed injury (48).

1. Animal Data

a. Electroencephalographic and Cerebromorphological Findings

Changes in the morphology of the brain and central nervous system have been observed in dogs exposed to high concentrations of CO over extended periods.

Lewey and Drabkin exposed six dogs to 115 mg/m^3 (100 ppm) CO for 5-3/4 hours a day, 6 days a week, for 11 weeks (56). The COHb level reached each day was about 20 percent. During the exposure, no changes were observed in the electroencephalogram (EEG) or in the function of the peripheral nerves. The dogs showed a consistent disturbance of postural and position reflexes and of gait. After exposure, morphologic examinations of the nervous system showed that all animals had sustained some cortical damage. No such findings were observed in the five control animals. There were also histologic changes in the white matter of the cerebral hemospheres, the globus pallidus, and the brain stem. These changes tended to follow the course of the blood vessels. A seventh dog, whose posterior coronary artery had been ligated 1 year prior to exposure, showed the most severe cerebral changes and had severe cardiac changes as well, even though he was exposed for only 18 days. Although it cannot be determined whether the observed changes are attributable to acute or chronic CO exposure, these results suggest that inadequate cardiac function may predispose to cerebral anoxia and thus increase the risk of brain damage from CO poisoning.

In dogs that were continuously or intermittently exposed to 58 to 115 mg/m^3 (50 or 100 ppm) of CO for 6 weeks, Lindenberg et al. (57) observed that the brain showed no areas of necrosis or demyelination. There was a mobilization of glia, however, which suggests that a disease process was under way; also, the lateral ventricles were enlarged. These investigators concluded that the brain changes were secondary to myocardial changes.

b. Behavioral Changes

Carbon monoxide has been found to induce behavioral changes in trained, unanesthetized, unrestrained rats (58,59). Some studies report alterations in simple learned performance in the rat. The animal usually performs in a box containing a lever the rat has been taught to press. For reinforcement, the food-deprived animal receives a food pellet when it presses the lever in a predetermined pattern.

In one series of experiments conducted by Beard and Wertheim (58), a low rate of response was differentially reinforced; that is, during certain periods, the animal had to refrain from pressing the lever for more than a predetermined fixed time in order for the next lever press to be reinforced. Mean data for six rats exposed to CO are shown in Figure 7-9. Exposure to CO never exceeded 48 minutes, and all

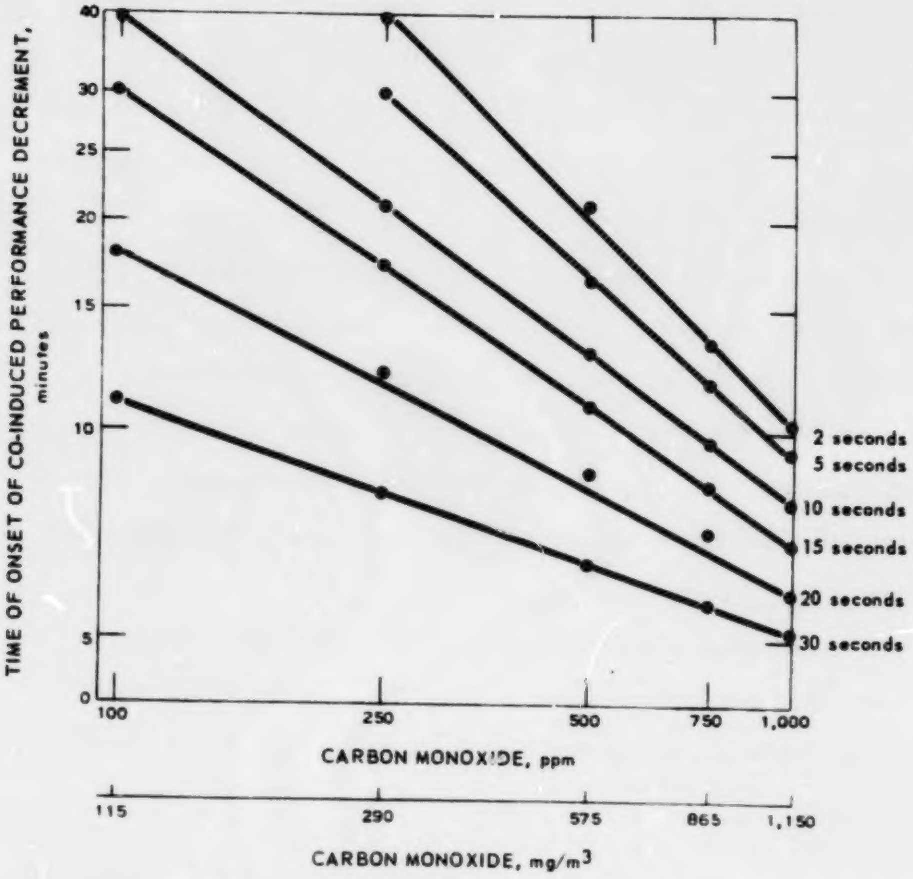

Figure 7-9. Effect of carbon monoxide on mean differentially reinforced response rate in rats (58).

experimental sessions, including control periods, lasted approximately 2 hours. Carbon monoxide decreased the performance on this schedule. Figure 7-9 gives the time of onset of a performance decrement large enough to fall at least 2 standard deviations below the rate measured during normal atmospheric conditions. The number to the right of each curve gives the minimum delay required of the animal for a response to be reinforced. For instance, perceptible effects were observed after exposure to 115 mg/m^3 (100 ppm) for 11 minutes when the minimum delay required was 30 seconds. It took 30 minutes of exposure to 115 mg/m^3 to produce the same relative decrement in response rate when the minimum delay was only 15 seconds.

More extensive testing, with exposure times ranging from 14 hours to 10 weeks, was done on rats and mice by Malorny, Fodor, and Pomp (60). The spontaneous activity of mice in an exercise wheel was checked after 14 hours in CO/air mixtures containing 64 mg/m^3 (55 ppm), 97 mg/m^3 (84 ppm), and 185 mg/m^3 (160 ppm). The distance run by animals exposed to 97 mg/m^3 was 50 percent less than that run by control animals, and, for those exposed to 74 mg/m^3, the distance run was 33 percent less. Conditioned responses and unconditioned flight responses of rats were tested after exposure to 174 mg/m^3 (150 ppm) for 14 hours daily (at night) over a period of 10 weeks. The animals had learned, prior to exposure, to escape an electric shock, administered via the wire mesh over which they ran, by jumping on a climbing bar (unconditioned flight response); or to execute this flight response upon hearing an audible signal that preceded the electric shock and to thereby avoid the pain stimulus (conditioned response). Just 4 weeks after the beginning of exposure, a number of the animals exhibited failure of the unconditioned flight response, while in 10 weeks, practically all of the animals completely lost the behavior they had previously been taught.

Xintaras et al. (59) have established that altered electrical activity in the cerebral cortex in rats can be observed after exposure to CO concentrations below those required to produce an impairment of performance. Six adult rats were fitted with implanted electrodes, one in the visual cortex and one in the superior colliculus. The stimulus used to detect changes in these areas was a light lasting 10 microseconds, flashed twice per second. A Skinner-type apparatus was used to monitor behavioral responses and was adjusted to reward each depression of the lever. When the rate of lever depression had stabilized, the flashes of light were initiated. Following an initial disruption of the lever-pressing activity, the light flash became informationally neutral and the rate of lever-pressing again became stable. When this point was reached, the rat was considered ready for the experimental procedure. Concentrations of 58 to 1150 mg/m^3 (50 to 1000 ppm) CO were used. A train of light flashes was presented to the rat while the lever was being pressed. Evoked potentials generated as a result of the flash stimuli were fed into an electronic monitoring system.

In an experiment in which the rat breathed 115 mg/m^3 (100 ppm) CO for 2 hours, no significant change in lever-pressing activity was detected when the animal was presented with a retractable lever. During this period, however, changes in the activity of the brain were recorded. These can be summarized as an increase in the amplitude of the primary component and a decrease in amplitude, with an increase in latency, of the secondary component. The increase in the amplitude of the first downward deflection was about 60 percent of the control value (compared with 80 percent in an experiment with 1150 mg/m^3).

At 58 mg/m^3 (50 ppm) for 1 hour, the amplitude increased by about 20 percent of control and the latency of the second component increased as well. At 58 mg/m^3 for 2 hours, these same effects were enhanced - about a 50 percent increase in amplitude of the first downward deflection. Repeated exposures to 58 mg/m^3 for 1 to 5 hours each day for 4 days resulted in a progressive deterioration of the secondary component and an associated increase in amplitude of the primary component. A post-exposure period of about 48 hours was required before these alterations in central nervous system activity returned to the pre-exposure baseline level.

In an extensive series of studies on the effects of chronic low-level exposure to CO, Stupfel (61) exposed mice to 58 mg/m^3 (50 ppm) for periods of 3 months to 2 years and compared results with those from appropria controls. Animals were placed in exposure chambers, in groups of 3 to 10 mice, for 5 days a week, 24 hours a day. No differences between treated and control mice were found with respect to fertility, fetal survival, body growth, food intake, weight and water content of various organs, heart rate, amplitude of the QRS deflection in electrocardiographic tracings, nocturnal output of CO from the animals, and blood chemistry (including hemoglobin, glucose, proteins, lipids, cholesterol, calcium, magnesium, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase). The lethal dose of a virulent strain of bacteria was the same for exposed and control mice. Similarly, no differences were found when exposed and control mice were first vaccinated and then challenged with a larger lethal dose of the same bacteria. Mice conceived and born in exposure or control chambers were enclosed in a small air-tight chamber. At the 30th and 53rd hour of the progressive hypercarboxic hypoxia, the mortality was the same for the mice born in either chamber. Growth of grafted tumors did not differ between exposed and control animals.

The same negative results described above were found when tests were repeated after 2 years of exposure to 58 mg/m^3 (50 ppm).

Back and Dominguez (62) performed a series of studies designed to show the effects of long-term CO exposure on task performance of trained monkeys. Twelve trained adult Rhesus monkeys were exposed to 55 mg/m^3 (48 ppm) CO in air for 100 days, and then to 55 mg/m^3 at a simulated altitude of 8230 m (27,000 ft) (5 psia in a two-gas system of 68 percent oxygen and 32 percent nitrogen) for 105 days. Successive study phases consisted of doubling the concentration of CO each 7 days following the last day of exposure to 55 mg/m^3, while maintaining the same simulated altitude. Thus, CO concentrations of 110 mg/m^3 (95 ppm), 220 mg/m^3 (190 ppm), and 440 mg/m^3 (380 ppm) were used. Tasks performed consisted of pressing levers in response to visual and auditory stimuli; avoidance of electrical shock provided the motivation to respond to the stimuli. All animals were trained on the tasks to a stabilized level during a period of several months prior to the CO exposure.

In the two experiments conducted at 55 mg/m^3 CO exposure, COHb saturation stabilized after the first 48 hours of exposure at 3.7 percent at sea level, and at 4.7 percent for a simulated altitude of 8230 m (27,000 ft). There was no observable decrement in performance under either sea level or higher-altitude conditions. Exposure to 110, 220, and 440 mg/m^3 resulted in mean COHb saturations of 8.3, 19.5, and 30.1 percent, respectively.

These levels produced performance decrements, in terms of reaction times and lever presses per minute, in only 2 of the 12 monkeys. Most animals performed well even when COHb levels of 30 percent saturation were attained and even though changes in appetite and outward appearance occurred in 6 of the 12 animals.

These results suggest that this stimulus-response pattern of a group of well-trained monkeys was apparently not altered by levels of COHb that are clearly detrimental to humans. It does not seem reasonable, therefore, to extrapolate these results to any possible human tolerance for CC

2. Human Data

There are several reports concerning the possibility that CO-induced impairment of higher nervous functions results in the impairment of human performance. One of the earliest of these experiments was conducted by Forbes et al. (63). They reported that eight normal men who were given simple performance tests simulating automobile driving were unaffected by exposure to CO until their blood COHb level reached 30 percent or more. The subjects felt normal at a COHb level of 30 percent; the two subjects who reached 45 percent COHb felt unable to drive a car and were near collapse, even though their test performance was only slightly impaired.

Schulte (64) has employed a number of psychological test procedures to determine whether any impairment can be observed at COHb levels lower than those that produce subjective symptoms. He has also sought the minimum level at which a measurable alteration in function can be detected. The following set of physiological and psychological tests was performed, and constitutes one testing cycle:

1. Pulse, respiratory rate, and blood pressure.
2. Color stimulus response test.
3. Letter stimulus response test.

4. COHb determination (Scholander and Roughton method).
5. Plural-noun underlining test.
6. Test of neurological reflexes.
7. Static steadiness test.
8. Arithmetic test.
9. Muscle persistence test.
10. *t*-crossing test.

Forty-nine healthy male adults aged 25 to 55 years were exposed to approximately 115 mg/m^3 (100 ppm) CO for exposure times sufficient to produce COHb levels ranging from 0 to 20.4 percent. These responses were evaluated during four consecutive testing cycles. The subjects did not know when they were being exposed to CO.

Table 7-2 gives the number of observations, the mean levels of response, the ranges of response, and the correlation coefficients between the specific measurement for each activity and the level of CO in the blood. Note that no correlation existed between percentage COHb

Table 7-2. RESULTS OF PHYSIOLOGICAL AND PSYCHOLOGICAL TESTS ON SUBJECTS EXPOSED TO 345 mg/m^3 (300 ppm) CO (64)

Test	Number of observations	Mean (range)	Correlation coefficient (between test and COHb level)
1. Pulse rate	156	72 (55-102)/min.	-0.047
2. Systolic blood pressure	156	122 (102-155) mm Hg	-0.004
3. Diastolic blood pressure	156	78 (55-90) mm Hg	-0.025
4. Respiratory rate	156	12 (9-17)/min.	-0.020
5. Muscle persistence time, left leg	156	27 (19-47)/min.	0.035
6. Muscle persistence time, right leg	156	28 (19-51)/min.	0.035
7. Letter responses	167	69.6 (49-98)/min.	0.001
8. Color responses	167	71.2 (51-99)/min.	0.078
9. Errors in letter response	167	18.0 (0-116)	0.906[a]
10. Errors in color response	167	18.7 (0-115)	0.847[a]
11. Completion time, plural-noun underlining	196	186.8 (87-317) sec	0.812[a]
12. Completion time, arithmetic	196	835 (501-1453) sec	0.665[a]
13. Completion time, *t*-crossing	196	123 (43-329) sec	0.792[a]
14. Errors in plural-noun underlining	196	17.7 (1-46)	-0.053
15. Errors in arithmetic	196	4.6 (0-12)	0.590[a]
16. Errors in *t*-crossing	196	3.4 (0-14)	0.539[a]

[a] Significant at the 0.001 level.

and any of the physiological activities or percentage COHb and reaction time on the simple choice response tests (No. 1 to 8, and 14). There was no apparent difference between the test results of the nonsmokers and those of the smokers, although Schulte considers the number of nonsmokers in his study to have been too small to permit statistically significant conclusions. No data on the smoking habits of the subjects were supplied in the report, nor was there any information on the basal COHb levels of these subjects.

When the results obtained from each of the tests were further divided into 20 groups according to COHb level (0 to 0.4; 0.5 to 1.4; 1.5 to 2.4 percent, etc.), it was found that the number of errors in tests 9 through 13, and 15 and 16 increased with increases in COHb level (Figure 7-10). Schulte was of the opinion that an effect should be detectable at a COHb level of between 2 and 3 percent. Scholander and Roughton's method for analyzing COHb does not provide precise differentiation at levels below 5 percent, however, and the low COHb categories used by Schulte therefore cannot be considered to be quite exact.

Grudzinska (65) studied EEG results and other parameters for 60 workers who were exposed to no more than 115 mg/m^3 (106 ppm) CO in their work areas. A control group of 30 workers similarly employed was also studied. The average COHb level was 7 percent in the exposed group (the level exceeded 10 percent in 11 subjects) and was 3 percent in the control group. In both groups, the smokers had higher COHb levels than the nonsmokers.

Electroencephalograms were made at rest and after unspecified activities. A neurasthenia syndrome, which was based on subjective complaints, was diagnosed in 63 percent of the exposed group and 40 percent of the control group; but there was a statistically significant increased incidence of headache and

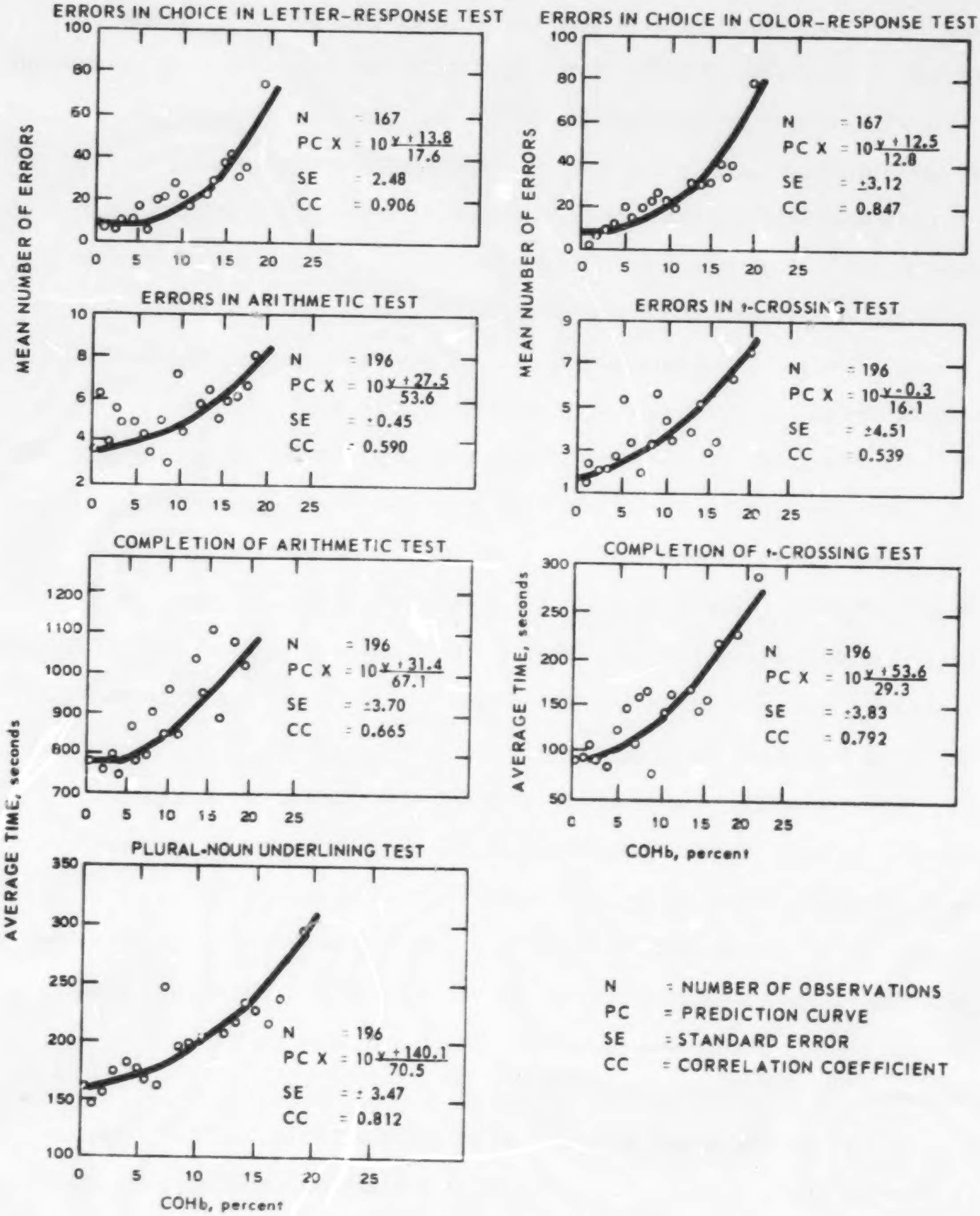

Figure 7–10. Effects of small concentrations of COHb on certain psychomotor tests(64).

general debility in the exposed group. A significantly higher proportion of shallow, low-voltage tracings with scanty alpha rhythm was found in the EEG's of the group exposed to CO ($p<0.01$). Since the neurasthenia syndrome had no well-defined clinical manifestations and because of uncertainty as to whether the investigation was a double-blind study, these data are difficult to interpret.

Beard and Wertheim have found that CO causes an impairment of time - interval discrimination (58). Their 18 subjects were young adult university students, all of whom were nonsmokers. The subjects, seated in a soundproof booth, were presented with a 1000-Hertz tone signal, the volume of which was adjusted to well above the auditory threshold. The first or "standard" signal was of 1-second duration, and the second or "variable" signal was modulated in 18 steps between 0.675 and 1.325 seconds. The subjects were asked to indicate whether the second signal was shorter, longer, or of the same duration as the first. The comparison stimuli were presented in blocks of 25 trials; 8 were identical, 8 longer, and 9 shorter than the standard. A total of 600 trials was presented to each subject in a single session, and each subject participated in at least 15 sessions.

Figure 7-11a shows the mean percent response after exposure to 0, 58, 115, 201, and 288 mg/m^3 (0, 50, 100, 175, and 200 ppm) CO. Each point on the graph represents the mean performance at each CO dose (based upon three determinations per subject) during the second and third hours of the session; that is, during 0.5 to 2.5 hours of CO exposure, since exposure bega after the first 0.5 hour. Comparison of performance in sessions during and prior to CO exposure revealed significant impairment by "t"-test at all doses ($0.01 <p< 0.02$ at 58 mg/m^3; $0.001 <p< 0.01$ at higher concentrations). When discrimination of the differences in the duration of

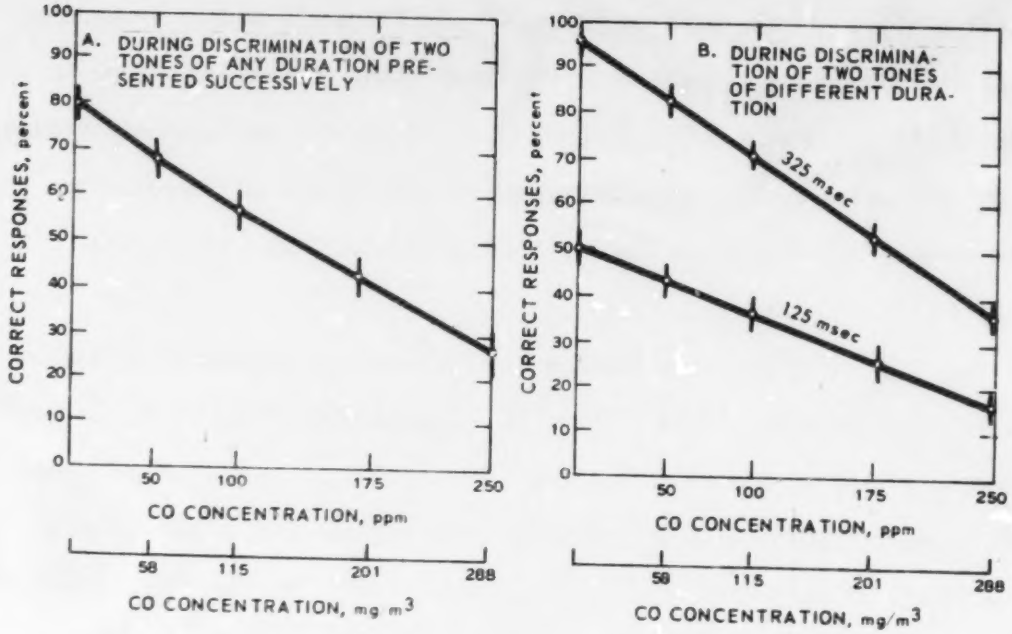

Figure 7-11. Mean percent correct responses (±one standard deviation) to 1,000-Hertz tone by 18 human subjects during exposure to carbon monoxide (58).

125 and 325 milliseconds was considered separately, the overall decrement for the latter was slightly greater (60 percent) than for the former (35 percent), as is shown in Figure 7-11b. The percentage of correct discrimination of differences in tone duration of 325 milliseconds was 95 percent at 0 mg/m^3 of CO, compared with 50 percent when the difference was 125 milliseconds.

Data for the time taken to obtain a significant impairment of auditory discrimination are shown in Figure 7-12. A fall in the percentage of correct responses was considered significant when the mean percentage of correct responses fell below two standard deviations of the mean performance without CO. Figure 7-12 shows that just 90 minutes of exposure to 58 mg/m^3 CO can produce such a response. Unfortunately, the blood COHb levels in the studies are not available; so that possible relationships between temporal

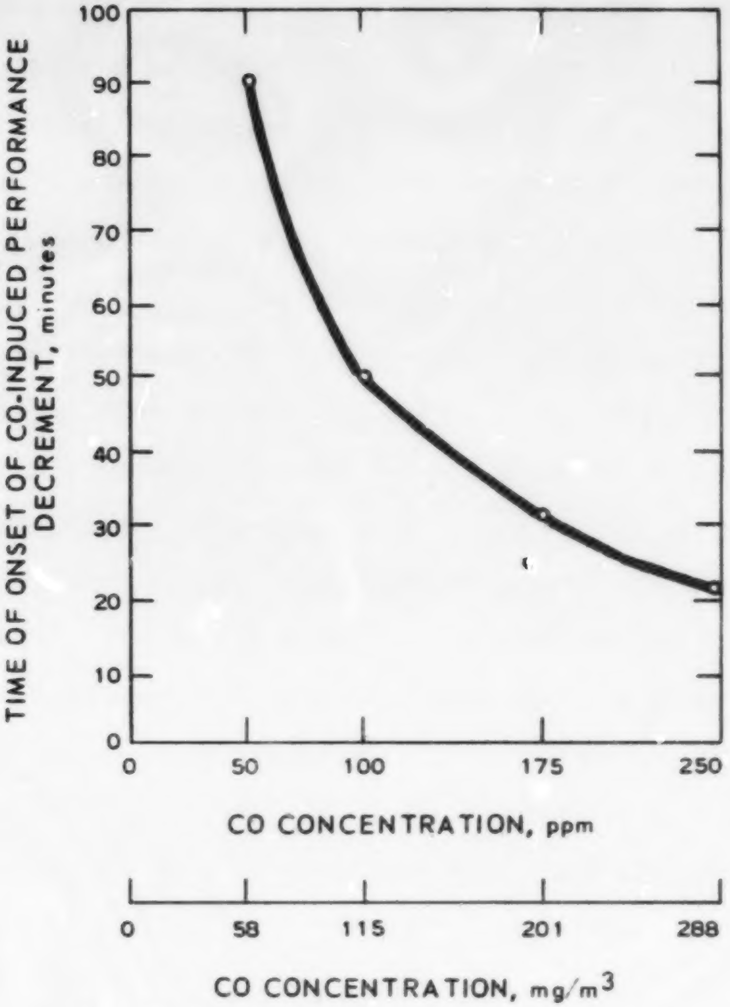

Figure 7-12. Time after initial exposure to each concentration of carbon monoxide at which mean correct response fell two standard deviations from mean correct response in absence of carbon monoxide (58).

impairment and COHb could not be measured directly. From the length of exposure and the concentrations given, an increase in COHb of about 2 percent can be inferred. Assuming a background level of approximately 0.5 percent COHb, an impairment in timing behavior can be expected to occur at COHb levels of about 2.5 percent.

Stewart et al. (66) exposed human volunteers to CO at concentrations of less than 1, 29, 58, 115, 230, 575, and 1150 mg/m^3 (less than 1, 25, 50, 100, 200, 500, and 1000 ppm). Studies were conducted in an air-conditioned exposure chamber in which CO concentrations were recorded continuously by an infrared spectrometer. Eighteen healthy males ranging in age from 24 to 42 years participated in the study. Only three of the subjects were smokers, and these subjects abstained from smoking for the duration of the study. Prior to and 16 hours after each exposure, blood samples were obtained for these analyses: a complete blood cell count, sedimentation rate, sodium, CO_2, chloride, potassium, calcium, total serum protein, alkaline phosphatase, bilirubin, blood urea nitrogen, glucose, serum glutamic-oxaloacetic transaminase, and COHb determinations. During CO exposures ranging from less than 1 to 115 mg/m^3, physiologic performance tests were periodically conducted during 8 hours of continuous exposure to the same CO concentration. These performance tests consisted of: hand and foot reaction time in the American Automobile Association (AAA) driving simulator, Crawford screw test, hand steadiness in the AAA steadiness test, Flanagan coordination test, orthorator visual test, and time-estimation hand-reaction-time test. The latter test consisted of a series of nine tone stimuli, followed by nine light stimuli of approximately 1, 3, or 5 second duration presented in a random sequence. At the termination of each stimulus, the subjects depressed a push-botton for an interval estimated by the subject to be equal in duration to the original auditory or light stimulus. Standard EEG and visual evoked response recordings were also obtained during exposure. Following each exposure, serial venous blood samples and simultaneous alveolar breath samples were collected for determination of COHb saturation and CO concentration.

No untoward subjective symptoms or objective signs of illness were noted during the 8 hours of exposure or in the 24-hour period following exposure. All of the clinical chemistries, including the repeat battery 16 hours after exposure, remained within normal limits. There was no detectable change from control values for any of the physiologic performance tests during an 8-hour constant CO exposure over the range of 1 to 115 mg/m^3. The latter concentration produced a blood COHb level of 11 to 13 percent.

Three subjects were exposed to 230 mg/m^3 (200 ppm) CO for 4 hours. COHb levels reached 24.8 percent within 2 hours and were associated with mild frontal headaches. All clinical chemistries remained within normal limits, but changes were observed in the visual evoked potential. The severity of headaches and changes in the visual evoked potential increased during 2 hours of exposure to CO concentrations of 575 mg/m^3 (500 ppm); this exposure produced COHb levels of 22 to 25.4 percent. During a final exposure, subjects were exposed to a constantly rising CO concentratio over 2 hours until a level of 1150 mg/m^3 (1000 ppm) was reached. This peak concentration was maintained for an additional 30 minutes, during which the COHb level reached 31.8 percent. Although severe headaches were reported, no changes in clinical chemistries or electrocardiogram (EKG) and no impairment of time-estimation ability were found. Performance on the Crawford collar-and-pin test deteriorated dramatically. Because subjects complained of marked fatigue of hands and fingers, the deterioration may have been the result of interference of CO with muscle function rather than with central nervous system function. Changes in the visual evoked potential were more marked than with previous exposures.

There is some question about the sensitivity of the hand-reaction-time estimation test used in the above study as a measure of performance response to CO exposure. The fact that test performance did not deviate from control even with a COHb level of 31.8 percent implies a marked degree of insensitivity, especially when noticeable fatigue of hands and fingers accompanied performance of the manual dexterity test under the same conditions. Thus, it is doubtful that these results can be used to refute the contrasting data obtained by Beard and Wertheim (58), who employed a different performance measure for time-interval discrimination and who found consistent deterioration of performance with CO exposures ranging from 58 to 288 mg/m^3 (50 to 250 ppm). The time-interval discrimination test of Beard and Wertheim appears to be sensitive to CO exposure, but the different measure of time estimation employed by Stewart et al. was evidently insensitive to relatively high COHb levels.

Nine male nonsmokers, ages 19 to 22 years, were exposed to CO concentrations of 0, 58, and 144 mg/m^3 (0, 50, and 125 ppm) for 3 hours in a dome-shaped enclosed environmental system by Mikulka et al. (67). Tests of psychomotor performance, including a time-estimation test, a tracking task, and tests of vestibular function (balance and coordination) were administered, utilizing a double-blind procedure. The exposure schedule was systematically varied to remove any effect resulting from training. The time-estimation test required subjects to estimate 10-second intervals on an electronic switch repeatedly for 3 minutes. Each series of tests was administered 6 times during a 3-hour exposure to each concentration of CO. When this series was finished, five subjects were exposed to 230 mg/m^3 (200 ppm) and three to 288 mg/m^3 (250 ppm), and the same tests were administered. Carboxyhemoglobin levels averaged 0.96, 2.98, 6.64, 10.35, and 12.37 percent in the group of subjects after 3 hours exposure to 0, 58, 144, 230, and 288 mg/m^3 (0, 50, 125, 200, and 250 ppm), respectively. One subject reported a slight headache during exposure to 288 mg/m^3 (250 ppm), but no other subjective symptoms were reported. Group performance scores obtained during each of the six times the tests were administered within the 3-hour exposure period were compared with CO exposure levels of 0, 58, and 144 mg/m^3 (0, 50, and 125 ppm). Exposures to CO, and the associated ultimate COHb levels of 2.98 and 6.64 percent, had no effect on tests of time estimation, tracking task, or vestibular function of the group. Within each exposure level, there was no group or consistent individual trend toward poorer performance on these tests over the course of the 3-hour exposure. The same pattern of negative results was reported for exposures to 230 and 288 mg/m^3 (200 and 250 ppm), although these results are not actually tabulated in the text of the report.

Important methodologic differences must be considered in the comparison of the results of the preceding three studies. Each group of investigators - Beard and Wertheim, Stewart et al., and Mikulka et al. - employed a different method for testing time estimation. In addition, the Stewart and Mikulka studies were conducted in a group setting in which elements of competition and other stimuli to performance were present. In the Mikulka study, external distractions that might compete for the attention of the study subjects were carefully eliminated or minimized. In contrast, individual subjects in the Beard and Wertheim study were tested in an isolated booth for 4 hours; boredom or fatigue may well have added to the effect of CO to produce deviations from baseline performance when exposure and nonexposure situations were compared. The stressful element of distraction, boredom, or fatigue has been demonstrated by Mackworth to be itself detrimental to human performance of repetitive tasks (68). The synergism between a stressful test situation, as may have been present in the Beard and

Wertheim study but not in the other two studies, and CO exposure at low concentrations may account for the differences in results. Thus, differences in the method for testing time estimation and differences in conditions under which the test was administered are possible reasons for the apparently contradictory results of these three studies. The relevance of the various study results to more complex modes of behavior, particularly to automobile driving, cannot be readily judged. Although Stewart et al. and Mikulka et al. did test more complex behavior, these tests were administered in a highly artifical setting. The failure to obtain significant changes from baseline even when COHb concentrations of 12 and 33 percent were reached suggests that the undistracted attention of the subjects to the experimental setting could overwhelm the possible subtle effects of CO on performance. The same phenomenon was observed by Forbes et al. (63) in the study of the influence of CO on the ability to drive automobiles. Two subjects who had COHb levels of 47 and 50 percent, respectively, were able to concentrate on their tests and perform reasonably well even though both reported that they were well aware that they were unable to drive a car; one of the subjects became unconscious for a few seconds after walking up a few steps during the test. Beard and Wertheim, on the other hand, tested a relatively simple performance task, but may have added a relevant factor, namely boredom or monotony. Apparently test method and test conditions must be considered when confirmatory studies are designed or when comparisons between studies are made. In this light, the results of these three studies are not contradictory. Until more evidence is obtained, each of the results must be considered to be highly specific to the method and conditions of testing, and extrapolations to other modes of behavior should be restricted.

Investigators other than Beard and Wertheim have reported deterioration of performance at low COHb levels. Ray and Rockwell (69) tested various automobile driving tasks performed by three young males at COHb levels of 0, 10, and 20 percent. The subjects were required to drive a car during night hours on an interstate highway while CO was administered to maintain one of the above COHb saturations. The subjects had been previously trained in the performance of each test procedure. Carboxyhemoglobin levels of either 10 or 20 percent increased the time needed to respond to tail light intensities (brakelight) and to changes in speed. These increases also altered their ability to maintain a constant speed of 65 miles per hour, to maintain a constant center-of-lane position, or to maintain a 200-foot separation from the car in front. Performance of these tasks required attention to multiple stimuli, some of which distracted the driver and prevented him from concentrating on any single task for prolonged time periods.

Beard and Grandstaff (70) recently reported the results of CO exposure on a second test of timing function. While individually isolated in a noise-insulated exposure chamber, seven subjects estimated the passage of 10- and 30-second intervals. Estimation of 10-second intervals was not affected by CO exposure. A highly significant dose-related performance decrement occurred, however, when subjects tried to estimate 30-second intervals. Exposures of 64 minutes at 58 mg/m^3 (50 ppm) produced significant impairment. In the same report, studies of Wertheim on the effects of CO exposure upon visual performance were reported. Four tests of visual function at various levels of brightness were conducted. Four subjects were exposed in random order to CO concentrations of 0, 58, 173, and 288 mg/m^3 (0, 50, 150, and 250 ppm), for a total exposure time of 1 hour on each test day. Exposures were always preceded and followed by performance testing without CO. Subjects were individually isolated in exposure booths for a period of 2-1/2 hours on each study day. Results of these studies, shown in Table 7-3, indicate consistent impairment of visual performance for three of the four measures of visual function. Carboxyhemoglobin levels were estimated from expired air samples. At each CO concentration, there was a rapid recovery in performance subsequent to the exposure; test results returned to normal more quickly than did the CO concentrations in the expired air.

Table 7-3. EFFECTS OF VARYING CO EXPOSURE ON VISUAL PERFORMANCE(70)

Test of visual performance	CO exposures producing significant impairment: Concentration, mg/m^3	Concentration, ppm	Time, min.	Estimated COHb level, %	Degree of impairment, %
Relative brightness threshold	58	50	49	3.0	4.4
	173	150	17	3.0	5.0
	173	150	49	5.0	8.0
	288	250	17	4.0	3.6
	288	250	49	7.0	8.6
Critical flicker fusion frequency	58	50	50	3.0	5.0
	173	150	50	5.0	8.0
	288	250	50	7.5	2.0
Visual acuity	58	50	27	3.0	5.5
	58	50	60	3.3	17.5
Absolute threshold for light	0 to 290	0 to 250	17 to 60	—	No consistent effect

Bender et al. (71) exposed 42 subjects (27 female, 15 male) to 0 or 115 mg/m^3 (0 or 100 ppm) CO for about 3 hours in an exposure chamber with a capacity of 1.5 m^3. The subjects had to take an extensive battery of psychological tests while their COHb levels were 7 percent. The tests included, but were not limited to the following: intelligence tests (Amthauer's IST), three tests to determine perception speed (recognition of letters, number of points, and symbols presented by a tachistoscope), learning ability and memory, the learning and retention of nonsense syllables, and a dexterity test (Purdue peg board) with and without a secondary task.

Significant impairment of performance produced by CO was found in the following: letter recognition during tachistoscope viewing (perception speed), backwards repetition of numbers (short-term memory), Purdue peg board (manual dexterity), and the learning of nonsense syllables (learning ability). In the intelligence test, significant impairment resulting from CO was found only in one of six subtests (abstraction ability).

These findings supplement those previously reported to the extent that they show that COHb levels between 5 and 10 percent can apparently also cause impairment of cognitive performance. There are certain difficulties connected with interpretation, however, because the observed effects could be completely the result of a CO-induced reduction in alertness in the execution of testing; that is, the result of concentration disturbances. Such CO-induced concentration disturbances related to the reduction of wakefulness have been objectively studied by means of so-called vigilance tests. Vigilance tests are trial setups in which subjects must discover infrequent and random signals near threshold values in a low-stimulus milieu. The percentage of missed or discovered signals is usually taken as the measure of performance.

Groll-Knapp et al. (72) exposed 20 subjects of both sexes to concentrations of 0, 58, 115, and 174 mg/m^3 (0, 50, 100, and 150 ppm) for 110 minutes and had them take an auditory vigilance test during the last 60 minutes of exposure. The researchers were able to show that the omission quotient (percentage of signals not heard) increased linearly with CO exposure and that significantly more response-inducing signals were missed at just 58 mg/m^3 than under control conditions. Moreover, a linear, negative correlation was found between the level of CO and the amplitude of aurally induced potentials that occurred in the EEG synchronously with the stimuli.

Fodor and Winneke (73) exposed 12 male and female nonsmokers to a CO concentration of 58 mg/m^3 (50 ppm) for 5 hours and had them take an auditory vigilance test between the 89th and 225th minutes, interrupted by a brief pause after 45 minutes of testing in each case. Between the 89th and 125th minutes of exposure, significantly more critical signals were missed with CO than under control conditions; delay periods were also appreciably lengthened. During further vigilance testing, however, the exposure values were generally identical to the control values. Before vigilance testing was begun and after it was terminated, the subjects were given an extensive battery of psychomotor-performance tests, in which the speed and precision of motor operations of varying complexity were checked. No decrement in performance of these psychomotor tests was seen after CO exposure.

McFarland et al. (74) used a visual discriminometer to test effects of CO and altitude on visual thresholds of trained male subjects aged 16 to 25. In this test, the subject looked through a microscope and fixed on a red point of light on an illuminated background. Measurements were made of the lowest intensity of light, presented in flashes of 0.1 second, that could be distinguished against the background. Carbon monoxide or gas mixtures containing different percentages of oxygen to simulate various altitudes were administered through a closely fitting mask during the test. The concentration of COHb in finger-prick blood at the beginning of the experiment and 10 to 15 minutes after each CO administration was determined by the microgasometric method of Scholander and Roughton.

Carboxyhemoglobin level during CO administration ranged from 5 to 20 percent. As shown in Figure 7-13, the visual threshold increased (that is, the light had to be more intense to be distinguished against the background) as COHb levels increased over the entire range of exposure. The effects of CO hypoxia and simulated altitude were practically equivalent in this test; that is, the effect of a given COHb level was the same as that of an equal percentage loss of O_2Hb from high altitude. These results clearly showed changes in visual threshold at COHb levels as low as 5 percent; the same magnitude of change in visual threshold was produced by a simulated altitude of approximately 2450 m (8000 ft).

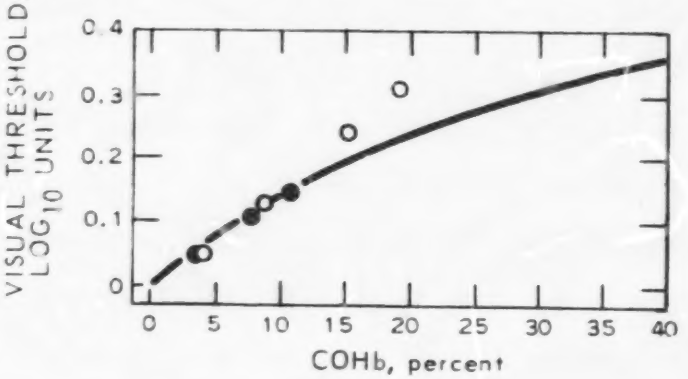

Figure 7-13. Relation between carboxyhemoglobin and visual threshold (74).

3. Discussion

Various data on the effects of low CO concentrations upon psychological and psychomotor functions appear contradictory. This is particularly true of the studies on time perception. Although Beard and Wertheim, as well as Beard and Grandstaff, were able to demonstrate significant CO-induced impairment even at COHb levels of about 2.5 percent (estimated from CO concentration and exposure time), Stewart et al. and Mikulka et al. did not detect comparable effects even at COHb levels above 15 percent. Only some of the studies by Stewart, Mikulka, and Beard and Grandstaff are directly comparable in terms of methodology. Stewart et al. and Mikulka et al. used maximum intervals of 10 seconds, while Beard and Grandstaff introduced intervals of 10 and 30 seconds. The described concentration-dependent CO effects could only be observed for the 30-second intervals. Thus, the sensitivity of time estimation to low CO concentrations appears to increase with the length of the intervals to be reproduced. The work of Beard and Wertheim, however, is also supported by the results of Groll-Knapp et al. on CO-induced impairment of performance in vigilance tests and by the results of Fodor and Winneke.

Complex performance tests, such as the psychomotor type, have proved to be quite insensitive to the effects of CO, as indicated by the work of Stewart et al., Mikulka et al., and Fodor and Winneke. A high level of motivation in the subjects may influence the test results. These factors are less important in the testing of simple sensoriphysiological functions. Such considerations may also explain why the studies by McFarland et al. and those of Wertheim on the CO-induced impairment of visual function indicated the same effects even at COHb values of about 4 percent.

The extent to which the CO effects discussed here permit conclusions to be drawn regarding the behavior of persons exposed to CO - for example, in street traffic - must remain an open question for the present. It should be emphasized, however, that these results must be considered highly specific for the test methods and conditions. External stimuli should probably be studied along with CO exposure. Future studies should therefore include the effects of external factors such as noise, fatigue, boredom, and other distractions, and should also evaluate the possibility of an interaction between such stimuli and test performance, which is assumed to be affected by CO exposure.

Since it has been adequately demonstrated that subjects who smoke cigarettes usually exhibit measurable and possibly significant increases in COHb level, it is important that studies be conducted either on nonsmokers or on individuals whose exposure resulting from smoking is clearly defined and whose initial COHb levels have been determined. It is presently still uncertain how much smokers are able to adapt to relatively prolonged rises in COHb level.

F. EFFECTS OF CARBON MONOXIDE ON THE CARDIOVASCULAR SYSTEM

Metabolic studies provide a good foundation for assessment of toxic effects of CO on the cardiovascular system. Myocardium extracts nearly all available oxygen from coronary blood even at rest. Increased oxygen demands caused by stress, such as exercise, can be met only by increasing blood flow through the coronary circulation. When oxygenation of the myocardium is inadequate, anaerobic pathways of metabolism are used at the price of decreasing efficiency markedly and increasing the likelihood that the heart's electrical conduction system will malfunction (75). Hypoxia has also been shown to influence metabolism of blood vessel walls (76,77), resulting in the accelerated formation of atheromatous changes. Many investigators have pursued these leads in studying the effects of carbon monoxide-induced hypoxia on cardiovascular function in a variety of experimental settings, including acute and chronic animal exposures, controlled human exposures, and epidemiologic studies of urban or occupationally exposed populations.

1. Animal Data

As long ago as 1936, Miura (78) determined that cardiac output increased and arteriovenous oxygen differences decreased with increasing carboxyhemoglobin concentrations in rabbits. These observations were, in general, confirmed by Chiodi et al. (79) in dogs and in men.

More recently, Lindenberg (57) compared the effects of hypoxia induced by CO and by low-oxygen gas mixtures. He exposed 27 dogs to concentrations of CO greater than 1150 mg/m^3 (1000 ppm) for 1 to 4 hours. A second group of 11 dogs was exposed to an air-nitrogen mixture producing an oxygen deficit equivalent to that caused by CO inhalation. In animals exposed to CO, the COHb levels reached 37 to 40 percent. In all EKG's recorded (on 13 out of 27 animals), a depression of the R-wave, elevation of the ST segment, an occasional increase in the T-wave, and deepening of the Q- and S-waves were observed. In some animals, these changes in EKG and associated irregularities of the heart action (premature ventricular contractions resulting in the abolition of arterial pulsation) persisted for several days. In dogs subjected to severe hypoxia, the EKG changes were essentially the same as those seen in dogs exposed to CO. At autopsy, the hearts of several animals revealed dilatation of the ventricles, especially the right one. In four CO-exposed and two hypoxic animals, small areas of muscle necrosis were observed, as well as fine granular fatty degeneration of muscle fibers in certain areas, particularly in the interventricular septum and in the outer wall of the right ventricle. Ehrich (80) found similar, though less definite, changes in dogs exposed chronically to lower levels of CO. The COHb levels reached in his experiments ranged from 2.6 to 12 percent.

Lindenberg (57) also exposed 15 dogs to 58 mg/m^3 (50 ppm) CO for 6 weeks. Seven of the dogs were exposed for 6 hours a day, 5 days a week. Eight were exposed continuously for 24 hours a day, 7 days a week. A second group of eight dogs was exposed to 115 mg/m^3 (100 ppm) CO on a similar schedule, four intermittently and four continuously. Five dogs were used as controls. All dogs were sacrificed a few days after the end of the experiment. The dogs exposed to 58 mg/m^3 developed blood COHb levels of 2.6 to 5.5 percent. There were no changes in the hemoglobin content or hematocrit. Five intermittently and five continuously exposed dogs developed EKG changes during the third week similar to, but less severe than, those observed from short-term exposures to higher concentrations. Higher COHb levels in dogs after exposure to 58 mg/m^3 (50 ppm) CO were reported by Musselman et al. (81) in another study (see below).

The dogs exposed to 115 mg/m^3 developed COHb levels of 7 to 12 percent. Somewhat higher COHb levels would have been expected in man after similar exposures (57). All dogs showed abnormal EKG recordings after about 2 weeks, with depression of the R-wave voltage, elevation of the ST segment, occasional deepening of the Q-wave, and occasional premature ventricular contractions. At autopsy, the most frequent finding was a dilatation of the right heart chambers, and also, occasionally, of those on the left side of the heart. Histologically, muscle degeneration was found in some hearts.

In contrast, Musselman et al. (81) exposed 100 rats, 40 rabbits, and 4 dogs to 58 mg/m^3 (50 ppm) CO for 24 hours a day, 7 days a week, for 3 months. No changes were noted in the EKG's or in the pulse rates of the dogs Moreover, pathologic examination of organs and tissues revealed no differences between exposed and control animals in any of the three species. The average COHb levels reached were 7.3 percent for dogs, 3.2 percent for rabbits, and 1.8 percent for rats. The dogs had significant increases in hemoglobin levels (12 percent), hematocrit (10 percent), and red blood cell (RBC) counts (10 percent). It should be noted that the increase in the RBC count in one dog alone accounted for over half of the total increase established by the whole group (Table 7-4).

Table 7-4. PERCENT CHANGE IN BLOOD VALUES OF INDIVIDUAL DOGS IN RESPONSE TO 58 mg/m^3 (50 ppm) CO INHALATION DAILY FOR 3 MONTHS(81)

Dogs	Dog ID number[a]	Hemoglobin	Hematocrit	RBC count
Unexposed	191	-2	-6	-2
	192	-2	-5	-5
Mean		-2	-5.5	-3.5
Exposed	124	+7	+5	+6
	185	+10	+8	+4
	188	+14	+14	+8
	193	+16	+11	+22
Mean		+11.75	+9.5	+10.0
Statistical significance of change		$p < 0.05$	$p < 0.10$	

[a] Each line of data is from a single animal.

Roussel et al. (82) have detected reversible EKG changes in rats exposed to CO. Rats were exposed to 17 and 58 mg/m^3 (15 and 50 ppm) CO for 24 hours a day for 3 months. The exposures to 58 mg/m^3 caused a slight decrease in the QRS voltage during the first 2 weeks of exposure; this subsequently returned to normal despite continued exposure. No changes in heart weights were observed. Although there were increases in hemoglobin level, hematocrit, and RBC counts, they were significant only at the p = 0.10 and p = 0.15 levels.

The effects of acute high-level and chronic low-level CO exposure on cardiovascular and cerebral function and morphology in dogs has been studied by Preziosi (83). Acute exposure to CO concentrations exceeding 1150 mg/m^3 (1000 ppm), and producing maximum COHb levels of 3 to 40 percent, resulted in high mortality and, in survivors, sudden rises in cerebrospinal fluid (CSF) pressure and changes in EKG's (consisting of depression of R-waves, elevation of the ST segments, and deepening of the Q-waves). Major voltage depression and complete abolition of electrical potentials of the EEG occurred only after the EKG showed severe changes. No gross pathology was observed in the brains of surviving dogs, but histologic alterations were noted, ranging from microglial reactions to extensive necrosis of the white matter. In the heart, small areas of muscle necrosis and fine granular fatty degeneration of muscle fibers were found. Chronic intermittent and continuous exposure of 15 animals to 58 mg/m^3 (50 ppm) CO and of 8 animals to 115 mg/m^3 (100 ppm) CO for 6 weeks resulted in EKG changes similar to, but of lesser magnitude than, the changes in the majority of dogs in the acute exposure studies. Carboxyhemoglobin concentrations reached 2.6 and 5.5 percent in dogs intermittently or continuously exposed to 58 mg/m^3 (50 ppm), respectively, and 7 and 12 percent, respectively, in the dogs exposed to 115 mg/m^3 (100 ppm). At autopsy, the most frequent finding was a dilatation of the right cardiac chamber and dilatation of the lateral ventricles of the brain.

Vascular lesions caused by acute CO poisoning were first described by Klebs (84) in 1865. He observed hemorrhages in pericardium, endocardium, and tips of papillary muscles, as well as degenerative changes in vessel walls. Rosenblath (85) observed arterial wall thickening with endothelial proliferation and fatty degeneration.

Astrup, Kjeldsen, and Wanstrup (86) demonstrated that rabbits fed cholesterol-enriched diets had a more accentuated development of aortic atheromatosis when exposed to CO than found in the control group breathing air. Cholesterol-fed rabbits continuously exposed to CO for 10 weeks (with exposure levels sufficient to produce COHb levels of 15 percent for 8 weeks and 30 percent in the last 2 weeks) developed cholesterol deposits in aortic tissue at a rate 2.5 times faster than nonexposed cholesterol-fed animals. Intermittent CO exposures for 8 hours a day for 10 weeks (sufficient to produce COHb levels of 20 percent) resulted in a fivefold excess in the cholesterol content of aortic tissue of exposed versus control rabbits. Cholesterol feeding and hypoxia (10 percent oxygen in nitrogen) produced similar effects, but to a lesser degree. Carbon monoxide exposure without cholesterol feeding induced arterial lesions consisting of endothelial hypertrophy and proliferation and focal subintimal edema; these lesions could not be distinguished from those associated with arteriosclerosis occurring spontaneously in rabbits. The authors speculated that CO or hypoxia enhanced the development of atheromatosis by increasing vascular permeability to lipoproteins. This and more recent work by these and other authors is well summarized in a thesis by Kjeldsen (87).

The extensive scientific literature concerning the effects of carbon monoxide on cardiovascular function in animals, confirms that levels of 20 percent COHb or greater cause definite changes in EKG, hemodynamics, cardiac morphology, and vascular structure. In addition, there is the suggestion that much lower levels of COHb may be associated with similar but less easily demonstrable changes. More important, these animal studies have provided the necessary background for human clinical and epidemiologic studies.

2. Human data

Chevalier, Krumholz, and Ross (88,89) observed that smokers incurred a greater oxygen debt following exercise than nonsmokers did. Oxygen debt is defined as the increase in oxygen uptake after exercise has ceased compared to oxygen uptake before exercise. Because Chevalier and his coworkers suspected that the CO in cigarette smoke was responsible for the increased oxygen debt in smokers, they tested the hypothesis directly (90). Ten nonsmokers were exposed to 5750 mg/m^3 (5000 ppm) CO in air for 2.5 to 3.5 minutes, which resulted in 3.95 ± 1.87 percent COHb compared to 3.50 ± 1.80 percent COHb in a control group of nine smokers. A standard exercise test of 5 minutes on a bicycle ergometer with the same work load was administered to each of the 10 subjects before and after exposure to CO. Measurements of oxygen uptake were obtained at 30-second intervals during a 4-minute period of rest, during the 5-minute period of exercise, and for 10 minutes following exercise. Continuous EKG recordings were obtained and pulmonary function tests were made before and after exposure to CO. Following exposure to CO, the ratio of oxygen debt to increased oxygen consumption was greater ($p<0.05$) than before exposure to CO. Mean heart rate was significantly less after CO, both at rest and during exercise. In the pulmonary function tests, significant differences ($p<0.05$) occurred in maximum voluntary ventilation, respiratory capacity, total lung capacity, and ($p<0.005$) CO diffusing capacity (DL_{CO}). The change in DL_{CO} would be expected as a result of increased "back-pressure" accompanying elevated COHb levels. Chevalier and his coworkers thus showed that CO alone can account for the increased oxygen debt measured in smokers.

Ayres et al. (91) studied cardiorespiratory responses of five subjects after brief exposures to high levels of CO. Intracardiac pressures and mixed venous blood samples were obtained by means of a cardiac catheter positioned in the main pulmonary artery. Oxygen tensions were measured before. and 5 to 7 minutes after inhalation of 0.4 percent (4600 mg/m^3 or 4000 ppm) CO in air. The data are shown in Table 7-5.

Table 7-5. HEMODYNAMIC AND RESPIRATORY RESPONSES OF FIVE SUBJECTS TO CO INHALATION(91)

Subject	COHb, %	Pressure, mm Hg				A-V diff[e] percent by volume	Cardiac output, liters/min.	Vent,[f] liters	P_{CO_2},[g] mm Hg
		LA[a]	PA[b]	P_{aO_2}[c]	P_{vO_2}[d]				
1–									
Before	0.48	28	9	89	45	3.40	5.23	4.23	34
After	8.84	28	9	81	42	3.82	4.46	4.23	36
2–									
Before				86	37	3.96	4.37	4.68	36
After	6.29			80	30	4.55	4.35	5.72	36
3–									
Before		3	14	74	42	3.92	4.31	2.55	36
After		3	12	68	37	4.24	4.17	3.11	40
4–									
Before	0.37	9	13	84	49	4.00	5.32	5.43	39
After	4.95	9	13	79	42	4.66	6.54	7.36	38
5–									
Before	0.96	7	12	77	41	4.02	6.00	4.87	36
After	9.69	11	18	72	35	4.81	4.68	4.24	39

KEY:

[a] LA = Left atrium (wedge).
[b] PA = Pulmonary artery (mean).
[c] P_{aO_2} = Arterial oxygen tension.
[d] P_{vO_2} = Mixed venous oxygen tension.
[e] A-V diff = Arterial-venous difference.
[f] Vent = Ventilation per square meter of body surface area per min.
[g] P_{CO_2} = Carbon dioxide tension.

Oxygen tensions of arterial and mixed venous bloods decreased an average of 7.3 and 13.3 percent, respectively, when the COHb rose to between 5 and 10 percent. The difference between arterial and venous blood, which reflects extraction of oxygen by the tissues, increased in all five subjects. In the fifth subject, who received the greatest amount of CO, the left atrial pressure rose and the cardiac output fell, indicating development of abnormal left ventricular function (such changes occur with the onset of congestive heart failure). Intracardiac pressures, cardiac output, oxygen consumption, and ventilation did not change in the remaining four subjects.

Ayres et al. (92) have also reported on a study of 26 patients, each of whom had a catheter placed in the ascending aorta and pulmonary artery. Samples of mixed expired air and arterial, mixed venous, and coronary sinus (venous) blood were obtained before exposure. The subjects breathed a mixture of 5 percent (57,000 mg/m^3 or 50,000 ppm) CO in air for a period of 30 to 120 seconds. Ten minutes after exposure, repeat samples of blood and mixed expired air were collected while the subjects breathed room air. Coronary blood flow was measured immediately before and 10 minutes after exposure.

Table 7-6 shows mean values for selected cardiorespiratory measurements in the 26 subjects before and after CO inhalation. The significant increase ($p < 0.01$) in average oxygen extraction ratio indicates a more complete extraction of oxygen from perfusing arterial blood in the presence of increased COHb. There was a mean decrease of 20 percent in the venous oxygen tension, and this can be associated with the increase in COHb concentration. The decrease in venous oxygen tension implies a similar decrease in tissue oxygen tension and suggests the possibility that

Table 7-6. SYSTEMIC CARDIORESPIRATORY MEASUREMENTS IN 26 SUBJECTS BEFORE AND AFTER CO INHALATION(92)

Measurements	Control mean	CO mean	F[a]	p[b]
COHb, percent	0.98	8.96		
Arterial P_{O_2}[c], mm Hg	81	76	22.1	<0.01
Venous P_{O_2}, mm Hg	39	31	94.5	<0.001
Arterial P_{CO_2}[d], mm Hg	40	38	4.2	<0.05
Ventilation, liters/min.	6.86	8.64	4.1	<0.05
Cardiac output, liters/min.	5.01	5.56	4.4	<0.05
Oxygen extraction,[e] ml/100 ml	4.30	4.56	2.7	<0.20
Oxygen extraction ratio[f]	0.27	0.32	31.2	<0.01
Alveolar-arterial O_2 difference	20	29	7.0	<0.05

[a] F = variance ratio calculated for paired data with interaction as denominator.

[b] p = probability that observed difference between control and CO means is due to chance.

[c] P_{O_2} = oxygen tension.

[d] P_{CO_2} = carbon dioxide tension.

[e] Oxygen extraction = arteriovenous oxygen content difference.

[f] Oxygen extraction ratio = oxygen extraction divided by arterial oxygen content.

interference with some cellular processes that are particularly sensitive to oxygen tension could have occurred. The decrease in the mixed venous oxygen tension was regarded as a major primary response to CO inhalation, and Ayres believed that other hemodynamic changes must be considered secondary. Associated increases in cardiac output were considered a compensatory mechanism for tissue hypoxia, since they resemble the physiologic response to hypoxemia.

Peripheral tissues normally extract about 25 percent of the oxygen present in arterial blood; the remaining 75 percent serves as a reserve supply for increased oxygen needs. The mixed venous oxygen tension is normally about 40 mm Hg, but during exercise it may drop to 20 mm Hg. In contrast, the myocardial oxygen requirements are such that, even at rest, 75 percent of the oxygen is extracted from the coronary circulation. Coronary venous blood is, therefore, only about 25 percent saturated, which corresponds to an oxygen tension of about 20 mm Hg. No substantial reserve of oxygen is available to tissue supplied by the coronary vasculature unless the coronary artery dilates in response to low oxygen tensions. The coronary circulation is thus capable of increasing the flow rate in response to increased oxygen needs, rather than increasing the percentage of oxygen extraction. Coronary vascular disease, however, may prevent an increase in coronary blood flow in response to need, and the myocardium may be forced to attempt to extract more oxygen at the expense of an already reduced coronary venous and tissue oxygen tension.

The responses of the myocardium to increased oxygen requirements induced by CO inhalation in patients both with and without coronary disease have also been studied by Ayres et al. (92), by means of an additional parameter for measuring the response to CO. During periods of insufficient oxygen supply, the citric acid cycle (Krebs cycle), important in glucose metabolism, is impaired; the utilization of pyruvate produced by glycolysis is decreased, which results in an accumulation of pyruvate in the cytoplasm and the resultant conversion of pyruvate into lactate. Increased cellular concentrations of lactate and pyruvate result in decreases in normal extraction of these metabolites from the coronary blood. The extraction ratio of either lactate or pyruvate can thus be a useful index for expressing oxidative metabolism; these parameters are relatively independent of arterial concentrations. (The extraction ratio equals the coronary artery concentration minus the coronary sinus concentration divided by the coronary artery concentration.) The extraction ratios for both metabolites range from 0.15 to 0.30 when oxygen is plentiful. During periods of inadequate oxygenation, however, extraction decreases, and lactate and pyruvate may actually be produced by the myocardium. Under these conditions, coronary sinus concentrations exceed arterial concentrations.

Myocardial metabolic studies were conducted on seven patients with noncoronary heart disease and four patients diagnosed as having coronary artery disease. All patients had a catheter placed in the proximal coronary sinus. The data from this study are shown in Table 7-7. In contrast to results obtained in the systemic gas exchange

Table 7-7. MYOCARDIAL METABOLIC MEASUREMENTS IN 11 SUBJECTS BEFORE AND AFTER CO INHALATION(92)

Measurements	Control mean	CO mean	F[a]	p
Group 1 – non-coronary heart disease (7 patients)				
COHb, %	0.95	9.00		
Q_M,[b] ml/min - 100 g	129	186	6.5	<0.05
Oxygen extraction,[c] ml/100 ml	11.84	8.89	52.7	<0.001
Oxygen extraction ratio[d]	0.75	0.64	42.1	<0.001
MVO_2,[e] ml/min - 100 g	14.3	15.9	0.4	
P_{csO_2},[f] mm Hg	21	17	2.9	<0.20
Lactate extraction ratio[d]	-0.01	-0.19	0.7	
Pyruvate extraction ratio[d]	0.28	0.24	0.3	
Group 2 – coronary heart disease (4 patients)				
COHb, %	0.66	8.69		
Q_M, ml/min - 100 g	102	127	0.5	
Oxygen extraction, ml/100 ml	12.71	8.82	34.7	<0.01
Oxygen extraction ratio	0.75	0.58	419	<0.01
MVO_2, ml/min - 100 g	12.9	11.3	0.5	
P_{csO_2},[f] mm Hg	19	17	12.9	<0.05
Lactate extraction ratio	0.12	-0.36	19.6	<0.05
Pyruvate extraction ratio	0.39	-0.07	25.6	<0.05

[a] F = variance ratio calculated for paired data with interaction as a denominator.

[b] Q_M = coronary blood flow.

[c] Oxygen extraction = arterio-coronary sinus oxygen difference.

[d] Oxygen, lactate, and pyruvate extraction ratios = respective extraction divided by arterial concentration.

[e] MVO_2 = myocardial oxygen consumption.

[f] P_{csO_2} = coronary sinus oxygen tension.

studies, the oxygen extraction decreased for both groups and could be correlated with an increase in COHb. The oxygen extraction ratio also decreased in each of the two groups (compared with an increase found in the systemic studies). Coronary blood flow increased significantly in the patients with noncoronary heart disease but did not increase in those with coronary heart disease. Lactate extraction ratios changed, reflecting lactate production, in both groups, but the change was statistically significant only for the patients with coronary artery disease. Figure 7-14 shows the responses of three representative subjects, one with coronary artery disease, one with mitral stenosis, and a third with emphysema. Changes similar to those already described occurred in the patients with mitral stenosis and coronary artery disease. The emphysematous patient was hypoxemic at rest (Pa_{O_2} = 47 mm Hg); and, when the COHb level increased 6 to 7 percent, there was an increase in coronary blood flow and a drop in the mixed venous and coronary sinus oxygen tensions from 20 mm Hg each to the extremely low levels of 12 and 2 mm Hg, respectively. It can be noted from the examination of Table 7-7 that the average blood COHb concentrations of all 11 subjects at the time these effects were measured were about 8.5 to 9 percent. From examination of Figure 7-14, however, it can be noted that at least two representative patients, those with coronary artery disease or emphysema, had blood COHb levels considerably lower than the average.

These studies suggest, therefore, that persons with coronary artery disease and emphysema may be particularly susceptible to exposures of CO that could lead to blood COHb levels above 5 percent, such as those that may be encountered in smoking or, less frequently, in community air pollution. Because in this experiment there was only a brief exposure to

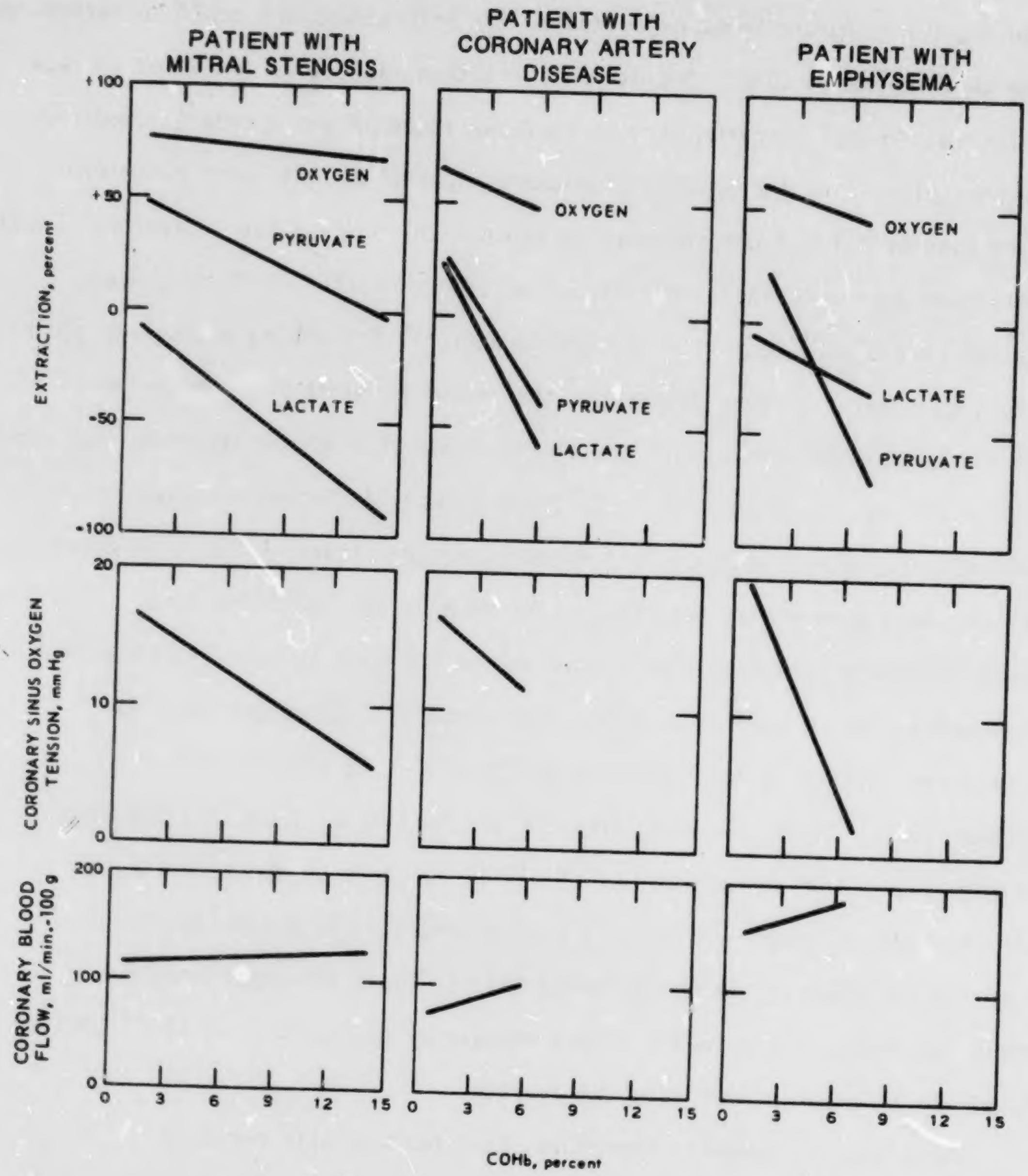

Figure 7-14. Myocardial metabolic measurements in three representative patients before and after carbon monoxide inhalation (92).

very high CO levels, the observed effects are difficult to relate to equilibrium conditions or longer exposures.

Both of Ayres' studies (91,92) show that increases in COHb lower arterial oxygen tension (Tables 7-5 and 7-6). The more recent one (92) also shows that the alveolar-arterial oxygen difference (A-aD_{O_2}) is increased (Table 7-6); this difference is an index of the inefficiency of oxygen transfer from the lungs to the blood. Brody and Coburn (93.) have recently shown, both theoretically and experimentally, that under some conditions an increased A-aD_{O_2} results from changes in the sigmoid shape of the O_2Hb dissociation curve induced by CO. These investigators have calculated the effects of 0 to 50 percent COHb on the A-aD_{O_2} under conditions of veno-arterial shunting and ventilation and perfusion imbalance, and have compared these effects to the effect of an equivalent degree of anemia (which does not alter the sigmoid shape of the O_2Hb dissociation curve). The results have indicated that an increase of 10 percent in the COHb causes an increase in the A-aD_{O_2} in the presence of shunts as small as 2 percent of the cardiac output, but there were no significant changes when the shunts were less than 1 percent of the cardiac output. The effect of an equivalent anemia was considerably less. The changes in A-aD_{O_2} with perfusion abnormalities were smaller than those with veno-arterial shunts, the effect of an equivalent anemia being less than that of increased COHb. The results of these calculations were verified experimentally by exposing five normal subjects, two patients with intracardiac shunts, and two patients with perfusion imbalance to sufficient CO to give an increase in COHb of about 10 percent. These results are tabulated in Table 7-8. Brody and Coburn consider that their findings have important implications, since the tissue hypoxia produced by increased COHb may be augmented by arterial hypoxemia in the presence of abnormal perfusion relationships or veno-arterial shunts. Arterial hypoxemia may play an important role in CO poisoning of subjects with normal lungs if they develop perfusion imbalance or veno-arterial shunts when unconscious.

Table 7-8. EFFECT OF CO ON ALVEOLAR-ARTERIAL OXYGEN DIFFERENCE (A-aD_{O_2}) IN NINE SUBJECTS AFTER EXPOSURE SUFFICIENT TO INCREASE COHb ABOUT 10 PERCENT(93)

Subject	COHb, %			A-aD_{O_2}, mm Hg		
	Initial		Final	Initial		Final
Normal subjects (5)	0.9		11.7	12.1		11.6
S D	±0.1		±4.7	±4.9		±5.9
p value		<0.005			>0.5	
Intracardiac shunts						
Subject 1	2.1		12.8	36.5		46.9
Subject 2[a]	1.0		12.7	56.7		62.8
Perfusion imbalance						
Subject 3	2.1		12.8	38.0		41.0
Subject 4	1.7		11.5	39.8		42.6

[a] 2,3-diphosphoglycerate was elevated in this patient, which suggests that the O_2Hb dissociation curve was shifted to the right. This shift might, in part, counteract the effect of COHb on the A-aD_{O_2}.

People with these abnormalities may therefore face unusual risks from exposure to CO.

Anderson et al. (94) have reported the possible contributions of CO to the production of myocardial ischemia and dysfunction in 12 normal young men (21 to 36 years old) and 25 clinically normal middle-aged men (41 to 60 years old). None of the subjects had a history of heart disease or lung disease, blood pressure greater than 160 systolic or 100 diastolic, anemia, or claudication. Standard six-lead EKG tracings were obtained at rest, during treadmill exercise to 85 percent of age-predicted maximal heart rate, and in the supine position for 5 minutes following exercise. In addition, systolic time intervals were determined from phonocardiograms and carotid pulse tracings taken immediately before and precisely 2 minutes following exercise. These procedures were initially performed on each subject, in a fasting state, in the morning. Smokers were required to refrain from smoking for 8 hours prior to the test. Following these procedures the subject had a light breakfast, then breathed 115 mg/m^3 (100 ppm) CO for 4 hours.

Pre-exposure mean COHb level for all subjects was 2.4 percent; post-exposure mean was 6.4 percent. Following exposure, exactly the same procedures were performed as before exposure.

The maximum heart rate attained during exercise did not differ significantly after exposure from the rate before exposure. Because, in this form of exercise, heart rate is closely related to myocardial oxygen consumption, the lack of difference between pre- and post-exposure rates confirms that the two exercise periods were of equal stress on the cardiovascular system. Both groups of subjects, however, achieved the maximum heart rate at lower treadmill work loads after CO. A lower total energy expenditure thus resulted from exercise producing equivalent cardiovascular stress after CO exposure.

No abnormal EKG was observed in the younger group before or after exposure. In the older group, 19 subjects had completely normal records before and after CO; however, some type of definite abnormality appeared at some time in 7 of the 26 older subjects. Subject 1 had a definite ischemic response to exercise which remained the same after CO exposure. Subjects 2 through 5 had objective ischemic changes in their tracings that were worse after CO than before. Subjects 6 and 7 had severe arrhythmias after CO that were either less severe or not present before exposure. Six of the 7 subjects with abnormal EKG tracings were smokers whereas only 3 of the 19 with normal tracings were smokers. Systolic time intervals showed no consistent significant changes related to CO exposure. These observations seem consistent with previous work demonstrating the association of CO exposure with both mechanical and electrical malfunction of the heart. They also seem consistent with the hypothesis that COHb levels similar to those that can result from exposure to urban air pollution can be associated with compromised myocardial function in a significant portion of the population.

On the basis of extensive animal and human data summarized here, it seems reasonable to assume that low-level, chronic exposure to CO may be associated with other increased risk factors in the development of systemic as well as coronary vascular disease. More acute, higher-level exposures may further compromise myocardial function in those persons with established coronary artery insufficiency. These hypotheses need extensive testing in a variety of experimental situations.

G. NONHEMOGLOBIN ABSORPTIVE SYSTEMS

1. Myoglobin

Because myoglobin and hemoglobin are structurally related, they can be expected to react with CO in a similar manner. Myoglobin, however contains only 1 heme moiety per molecule, so that the reaction occurs without the formation of intermediates. *In vivo*, the function of myoglobin may be to act as a reservoir for oxygen within the muscle fiber.

Rossi-Fanelli and Antonini (95) have recently studied the oxygen and CO equilibria of human myoglobin *in vitro* and have described a hyperbolic oxygen dissociation curve. The oxygen dissociation curve for myoglobin differs from that of hemoglobin in that it is not affected by the hydrogen-ion concentration, the ionic strength, or the concentration of the myoglobin. Both the shape and the properties of the oxymyoglobin (O_2Mb) dissociation curve reflect the difference in structure and function between myoglobin and hemoglobin. The relative affinity of human myoglobin for CO and O_2 is 40. Although it is not as high as that of hemoglobin, it is still sufficient to cause appreciable formation of carboxymyoglobin (COMb) in non-fatal CO poisoning.

The quantity of CO bound to myoglobin depends on the CO partial pressure in tissue. Measurements of CO partial pressure in tissue were done by Gothert et al. (96,97) in rabbits, guinea pigs, and rats exposed to CO concentrations from 99 to 1150 mg/m^3 (86 to 1000 ppm). Their study showed that the CO partial pressure in tissue is only about 50 percent of the CO partial pressure in the inspired air and alveolar air, once diffusion equilibrium has been attained (Figure 7-15). The three animal species differ considerably in the affinity of their hemoglobin for CO (98).

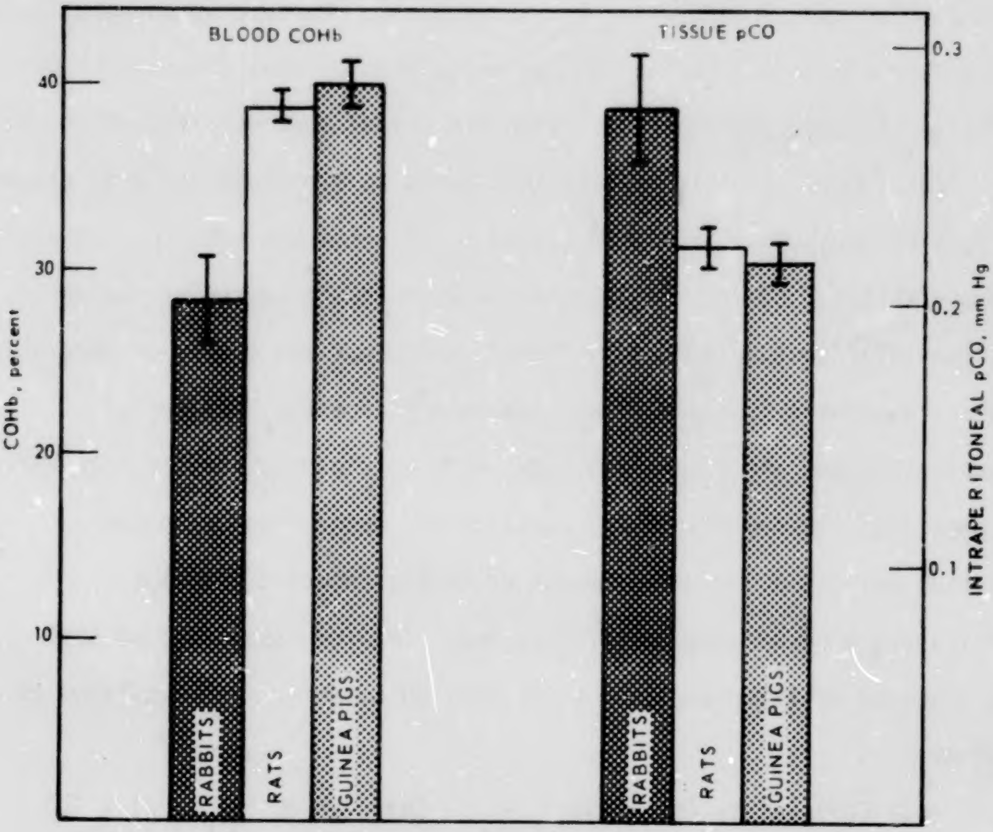

Figure 7-15. Carboxyhemoglobin concentration in blood and carbon monoxide partial pressure in tissue (i. p.) of rabbits, rats, and guinea pigs breathing 0.496 mm Hg carbon monoxide (805 mg/m^3 or 700 ppm). Average values obtained after diffusion equilibrium was reached (97).

The CO partial pressure in the tissues of animals decreases as the COHb value at equilibrium increases, so that it is ultimately a function of the CO affinity (Figure 7-15). These findings can be explained by the fact that the diffusion of CO to the tissue is substantially influenced by the delivery of CO by hemoglobin. This CO delivery results from the restoration of equilibrium among CO, O_2, and hemoglobin after oxygen has been delivered to tissue. Because this restoration of equilibrium is subject to the law of mass action, it is possible to calculate the CO partial pressure in tissue. This calculation confirms the findings established experimentally; in other words, the CO partial pressure in tissue amounts to some 50 percent of the CO partial pressure in the inspired air. Because human hemoglobin has a very high affinity for CO, the calculated partial pressure of CO in tissue is somewhat lower than with the animal species examined in this study

The proportion of inhaled CO that binds to myoglobin has been studied in dogs by Luomanmaki (99). In the calculation of his results, Luomanmaki assumed that the CO was equilibrated between an intravascular and an extravascular pool, and that the latter was comprised mostly of myoglobin. The extravascular CO capacity was determined from the difference between the separately measured total body CO capacity and the intravascular CO capacity. The total body CO capacity was determined using the dilution principle. A known amount of CO was injected into the inspiratory tube of a rebreathing system. The increase in blood COHb was measured at intervals, and total body CO capacity was calculated as follows:

$$\text{Total body CO capacity (ml STPD)} \quad = \quad \frac{\text{Injected CO (ml STPD)} \times 100}{\text{Increase of blood COHb}}$$

This equation assumes that the increase in COHb is estimated at the time when there is the most net transfer between the different CO pools. The measure COHb levels must be extrapolated to the time of CO injection to correct for any increase in COHb resulting from endogenous production of CO.

Data relating COHb values to extravascular CO capacities, half-times, and equilibrium time of CO transfer from the intravascular to the extravascular pool are shown in Table 7-9. The mean extravascular CO capacity was 22.9 percent of the total body CO capacity. There was no significant linear correlation between the extravascular CO capacities and the COHb levels, although only 3 of the 11 dogs had COHb levels exceeding 10 percent. The mean half-time to equilibrium between the two pools was 12.5 minutes, and the mean of the equilibrium times was 29.2 minutes. There was no linear correlation between either the half-time or the equilibrium time and the COHb level. The transfer of CO from the intravascular to the extravascular CO pool occurs within the time needed for circulatory mixing, as detected by ^{51}chromium-labeled red cells. The distribution of CO between intravascular and extravascular CO pools was independent of P_{O_2} in the P_{O_2} range of 65 to 440 mm Hg.

Studies conducted by Coburn (100), in which dogs were exposed to ^{14}CO, have demonstrated that identical CO exposures can produce different degrees of CO saturation of hemoglobin, depending on the partial pressure of oxygen in the blood and in the tissue. Coburn et al. (51) also determined the ratio of the CO content in the muscle tissue to the CO content in the blood ([COMb]/[COHb]) as a function of the arterial P_{O_2}, other conditions being equal. In the case of skeletal muscle, this ratio was shown to be 1.1 with normal arterial P_{O_2}, while with an arterial P_{O_2} of less than 40 mm Hg this ratio increases by a factor of 3.

Table 7-9. EXTRAVASCULAR CO CAPACITIES, HALF-TIMES, AND EQUILIBRIUM TIMES FOR TRANSFER OF CO FROM INTRAVASCULAR POOL TO EXTRAVASCULAR POOL, AND LEVELS OF BLOOD COHb AT END OF TRANSFER (99)

Dog No.	Extravascular CO capacity, % of total body CO capacity	Half-time of CO transfer, minutes	Equilibrium time of CO transfer, minutes	COHb,[a] %	Body weight, kg	Body myoglobin content,	
						g	g/kg body wt
1	14.6	14	35	5.35	12.9	28.4	2.20
5	29.0	9	19	10.50	15.0	60.0	4.00
6	20.9	18	45	0.75	15.9	44.0	2.77
7	17.5	12	30	30.95	16.4	35.8	2.18
9	16.0	12	28	1.16	15.5	35.1	2.26
10	16.3	14	33	7.42	15.9	32.8	2.06
11	15.6	8	17	35.00	15.0	26.9	1.79
12	31.8	8	15	2.54	13.2	55.2	4.18
14	37.5	8	22	2.32	10.6	36.6	3.45
18	27.5	17	40	2.42	17.5	83.5	4.77
21	26.0	17	37	5.00	13.6	46.3	3.40
Mean	22.9	12.5	29.2	–	14.68	44.05	3.01
S D	7.4	3.7	9.4	–	–	–	0.98

[a] COHb values extrapolated to the time of CO injection because of endogenous formation of CO.

Carbon monoxide saturation of myocardial myoglobin, with normal arterial P_{O_2}, is approximately 3 times that of skeletal muscle myoglobin. During hypoxia, the ratio increases to 6.1. A sample calculation based on these studies shows that in a person whose COHb content is approximately 7 percent, some 20 percent of the myocardial myoglobin is saturated with CO.

2. Cytochrome Oxidases

Cytochrome oxidases are hemoproteins that, *in vitro*, are capable of reacting with CO. The reaction between the heme moiety of these compounds and CO appears to be similar to the reaction of CO with hemoglobin and myoglobin. Reversible binding, photolysis, and competition between oxygen and CO are characteristics of cytochrome oxidases. The quantity of CO bound to these enzymes is a function of the CO partial pressure in the tissue (96,97), the O_2 partial pressure in the cell, and the relative affinity constant of the enzyme for CO and O_2.

Although all three types of cytochrome oxidases that are important in the oxygen consumption system of the mammalian cell can be blocked in some part by CO, only the terminal member of the electron transfer system (which is located in the mitochondria) combines with CO; the other members do not combine unless they are denatured. This terminal member is known as cytochrome a_3. The reaction between cytochrome a_3 and oxygen accounts for about 90 percent of the total oxygen consumption by the cell. In the presence of oxygen, the reaction of CO with cytochrome a_3 is competitive, and the CO uptake depends on the concentration of the enzyme and the ratio of CO to O_2, rather than on the concentration of CO alone. For 50 percent inhibition, the required ratio of CO to O_2 is between 2.2 and 28 (101-103). Because the ratio is usually so much lower, these conditions give oxygen a substantial advantage in competition with CO.

Nevertheless, the reaction of CO with this enzyme contributes substantially to the effects of CO poisoning, at least in severe cases. This was established by Bander and Kiese (104), who made measurements in isolated mitochondria. These authors made their measurements at CO pressures of between 0.3 and 1.5 mm Hg in the tissue. In the case of hypoxia induced by such CO poisoning, the respiration of the brain cells drops to an unacceptable level compared with hypoxemia resulting from any other cause. The studies made by Chance et al. (105), also dealing with isolated mitochondria, show that under certain conditions lower CO concentrations as well as higher ones (of the order of 115 mg/m^3 (100 ppm)) can have inhibiting effects on the cytochrome system in the mitochondria.

Another enzyme that can probably be blocked in vivo by CO is cytochrome P-450. This enzyme, located in the microsomal fraction of the cell, is the terminal member of the chain of mixed function oxidases that catalyze the incorporation of atmospheric oxygen into organic compounds and catalyze as well such reactions as the hydroxylation of acetanilide, the demethylation of codeine, and the hydroxylation of 17-hydroxyprogesterone at carbon-21. The experimental evidence that the CO-binding pigment of the microsomes is in the terminal oxidase of mammalian tissues was provided by Cooper et al. (106). These investigators reported that the ratio of CO to O_2 required for 50 percent inhibition is approximately 1:1 (range 0.5 to 1.5). Recently Rondia (107), using rats, was able to prove that the activity of the liver's benzopyrene-hydroxylase, which is probably coupled with cytochrome P-450, was inhibited by 10 to 25 percent following a 120-hour inhalation of 60 or 100 ppm CO.

When attempting to make an accurate evaluation of the toxicological significance of a partial blockage of cytochrome a_3 and cytochrome P-450, one must remember that while the intracellular P_{CO} never exceeds a value of several tenths of a mm Hg, intracellular P_{O_2} is also very low. Forster (108) estimated the intracellular P_{O_2} to be approximately 1 mm Hg in the mitochondria. _In vitro_, the minimum P_{O_2} for the function of isolated mitochondria is 0.5 mm Hg. For example, when inspiring 1150 mg/m^3 (1000 ppm = approximately 0.7 mm Hg) CO, a P_{CO} of approximately 0.35 mm Hg can be measured in the tissue at equilibrium (96,97). Because the rates of endogenous CO formation and CO metabolism are very low, little difference exists between the partial CO pressure found in the blood and in the cell organelles. As far as the total distribution in the organism of an inhaled CO dose is concerned, the enzyme-bound CO quantities are presumed to be small when compared with those bound to hemoglobin and myoglobin. Most of the useful information concerning the distribution of CO in the body has been summarized by Coburn et al. (52). Enzyme systems other than those mentioned may also be indirectly influenced by CO. Rozera and Fati (109) and Fati et al. (110) found a decrease in acid and alkaline phosphatase in erythrocytes as well as a reduction in activity of the erythrocyte phosphoglycomutase in rabbits exposed to 115 mg/m^3 (< 100 ppm) CO for several days. This observation must be interpreted as a consequence of a modified protein metabolism under the influence of CO rather than as a specific blockage of these enzymes. On the basis of all available data, no final judgment can be made on the toxicological significance of the blockade of enzymes by CO in mammalian cells.

H. EFFECTS OF CARBON MONOXIDE UNDER HYPOBARIC AND HYPERBARIC CONDITIONS

1. High Altitude (Hypobaric Conditions)

The effects of CO and of hypoxia induced by high altitude are similar. Most experimental data suggest that when high altitude and CO exposures are combined, the effects are additive. *In vivo*, there is an interaction between the two factors so that exposure to one may induce a physiological response that influences the response of the body to the other. For example, Forbes et al. (44) have shown that during light activity, their subjects had an increase rate of CO uptake at an altitude of 4880 m (16,000 ft) compared to that at sea level, because of the hyperventilation that results from the decreased P_{O_2}. When the ventilation rate was corrected to its value at sea level, the rate of uptake of CO decreased to a value within 10 percent of the sea level value.

Although the effects of hypoxia and CO appear to be additive, individually they do seem to produce different physiological responses. This is because they have different effects on blood P_{O_2}, on the affinity of O_2 for blood hemoglobin, on the extent of O_2Hb saturation, and on ventilation. The presence of COHb increases the affinity of hemoglobin for O_2, but lowers the total O_2Hb saturation. The ventilation rate appears to be influenced by receptors in the carotid and aortic bodies that are responsive to blood P_{O_2} and P_{CO_2} (111). Hypoxia results in a lowering of the P_{O_2} and increased ventilation ensues; in CO exposure, the P_{O_2} apparently does not change sufficiently to induce the necessary increased ventilation.

Several different physiological and psychomotor tests have been used to determine the effects of altitude with and without CO. Pitts et al. (112)

have observed the physiological responses to exercise when blood COHb levels were increased by 6 and 13 percent in a group of ten men at simulated altitudes (sea level, 2130, 3050, and 4570 m). The parameters measured were pulse rate, respiratory rate, and minute ventilation. A previous study had indicated that in subjects at rest the pulse showed no change with altitude up to 5030 m (16,500 ft). After regulated exercise at altitudes from sea level up to 6400 m (21,000 ft), however, the pulse showed a steep, almost linear, increase. Of the parameters measured in both these studies, mean pulse rate during exercise and for the 5 minutes immediately following exercise showed the closest correlation with blood COHb and ambient P_{O_2}. At sea level, an increase of 13 percent in COHb increased the mean exercise pulse rate from 105 to 112 and the recovery pulse rate from 91 to 98. An increase of 6 percent COHb had no effect at sea level; at 2130 m (7,000 ft), however, an increase of 6 percent COHb produced a significantly higher exercise pulse rate compared to that produced by altitude alone. Pitts calculated that for every 1 percent increase in blood COHb, up to 13 percent COHb, the increase in exercise pulse rate in normal subjects is equal to that which would be produced by a 100-m (335-ft) rise in altitude throughout the 2130 to 3050 m range (7,000 to 10,000 ft). It is likely that some of the subjects were smokers, since the group mean control COHb level ranged from 2.88 to 3.64 percent on different days. Since the smokers would have been preconditioned in part to the effects of CO, their responses to additional small quantities of CO might be expected to be lowered. This could have masked the additive effect of CO and hypoxia.

A more recent study has compared the effects of CO exposure and altitude (113). Eight healthy male subjects were divided randomly into two groups of four each; each group followed a different daily schedule. The subjects were briefly exposed daily for 10 days to concentrations of 5 percent CO (57,500 mg/m^3 or 50,000 ppm) at 4-hour intervals between the hours of 7 a.m. and 11 p.m. The doses were sufficient to give an average COHb level of 15 percent, although values ranging between 5 and 25 percent were recorded. A variety of circulatory, ventilatory, and renal function tests were performed during the course of the experiment. The same experimental protocol was also carried out on the same eight subjects after spending 10 days at an altitude of 3420 m (11,225 ft). This altitude gave, roughly, a degree of hypoxemia equivalent to that given by 15 percent COHb. The data obtained from the two studies are compared in Table 7-10. Of great significance are the circulatory and ventilatory responses to the two types of hypoxic conditions. As expected, CO hypoxemia shifted the O_2Hb dissociation curve to the left, whereas high altitude caused a shift to the right, the latter occurring during the first 24 hours. At increased altitude, both the cardiac output and the ventilatory rate increased within the first 24 hours, whereas CO had no consistent effect on these parameters.

The lowered arterial P_{O_2} at high altitude probably stimulated the chemoreceptors in the aortic and carotid bodies, with the resultant regulatory changes in ventilation. Mills and Edwards (114) have recently shown that these chemoreceptors are also stimulated during CO inhalation. These investigators have suggested that the lack of ventilatory response during CO hypoxemia is a result of depression of respiratory centers in the central nervous system. The effects of the two types of hypoxemia

Table 7-10. AVERAGE DATA FOR EIGHT SUBJECTS (DIVIDED INTO TWO GROUPS OF FOUR) TO COMPARE EFFECTS OF CO AND HIGH ALTITUDES ON VARIOUS PHYSIOLOGICAL PARAMETERS(113)

Test	Effect of 15% COHb	Effect of 3420 m altitude
O_2Hb saturation curve	Shift to left	Shift to right
Affinity of Hb for O_2	Increased (within 12 hr)	Decreased (within 24 hr)
Mixed venous oxygen tension, by estimation	10 to 20% decrease throughout exposure period	20% increase on first day, 10% decrease on second day, return to normal for rest of experimental period
Ventilation		
$\dot{V}_E$STPD[a] - rest	No change	15 to 20% decrease
- work	Slight increase on first day	Slight decrease
$\dot{V}_E$BTPS[b] - rest	No change	30% increase
- work	No systematic change	35% increase on first day; 50% increase by tenth day
Respiratory rate - rest	No change	15 to 35% increase
- work	No change	15 to 35% increase
Circulation		
P_{aCO_2}[c] - rest	Almost unchanged	Continuous decrease from 90 to 75% of control
P_{vCO_2}[d] - rest	Almost unchanged	Continuous decrease from 90 to 75% of control
Cardiac output	Group 1 increased 27% on first day, followed by return to normal; no change in Group 2	Group 1 increased 35 to 45% for the entire 10-day period; Group 2 increased 25% by fourth day and returned to normal by end of stay
Mixed venous-arterial CO_2 difference, by estimation - rest	Group 1 decreased 20% on first day; Group 2 showed no change	Group 1 decreased 15 to 20% for the entire 10-day period; Group 2 decreased on fourth day only
- work	Group 1 increased 20% percent on third and fifth days; no other changes noted	15 to 25% increase for the entire 10-day period
Renal function		
Glomerular filtration	50% increase on first day, return to normal on second day, remain within 20% of control for rest of experimental period	Very slight decrease, but close to control value

Table 7-10 (continued). AVERAGE DATA FOR EIGHT SUBJECTS (DIVIDED INTO TWO GROUPS OF FOUR) TO COMPARE EFFECTS OF CO AND HIGH ALTITUDES ON VARIOUS PHYSIOLOGICAL PARAMETERS

Test	Effect of 15% COHb	Effect of 3420 m altitude
Renal plasma flow	40% increase on first day, return close to pre-exposure value on second day, remain < 15% below control value for rest of experimental period	Very slight decrease, but close to control value
Diuresis	Increase of 400 to 500 ml	Increase to more than twice control by sixth day
Serum lipids (cholesterol)	No significant change for first 4 days; 6% increase in last 2 days ($p < 0.05$)	6 to 9% increase in first 2 days
Hematocrit	No change	Very slight increase (43.5 to 47)
Reticulocyte count	Threefold increase on third day; nearly fourfold increase by sixth day	Twofold increase on third day; nearly threefold by ninth day

$^{a}\dot{V}_{E}$STPD (liters/min) - ventilation at 0° C, 760 mm Hg, dry.

$^{b}V_{E}$BTPS (liters/min) - ventilation at body temperature and ambient pressure saturated with water vapor.

$^{c}P_{aCO_2}$ - alveolar carbon dioxide tension.

$^{d}P_{vCO_2}$ - mixed venous carbon dioxide tension.

at the cellular level can be estimated by comparing the P_{O_2} of the mixed venous blood under both circumstances, since this reflects tissue P_{O_2}. The data in Table 7-10 show that the average P_{O_2} of mixed venous blood in CO hypoxemia is lower than in hypoxic (high altitude) hypoxemia. In both types of hypoxemia, a lowered tissue P_{O_2} is expected; as indicated by the mixed venous P_{O_2}, this is more pronounced in CO hypoxemia. At increased altitude, the shift of the O_2Hb curve to the right and the circulatory and ventilatory responses compensate for most of the associated tissue hypoxia during the first 24 hours. Such regulatory mechanisms do not appear to be stimulated by CO hypoxemia, and hence the latter may be considered to be more of a physiological burden.

Other studies on the combined effects of CO and altitude have used psychomotor tests. Variable results have been reported, but some of these may be explained by the use of different tests and others by the lack of proper controls. The flicker fusion frequency (FFF) and the critical flicker fusion (CFF) tests, often employed in these studies, have recently been criticized because of their lack of reliability (115).

McFarland et al. (74) have used the increased threshold of visual perception as an index of the effect of both CO and high altitude. Although studies of visual perception have already been discussed in Section E above, it is pertinent to note at this point that McFarland et al. documented an impairment in visual perception in a single subject with a COHb of about 5 percent at sea level that was equivalent to the impairment associated with the low P_{O_2} at an altitude of 2130 m (7000 ft).

In another experiment, a group of four trained subjects was used to study the time course of recovery from CO and altitude (116). Data from a single subject suggest that it takes longer to recover from a given COHb level than from an equivalent lowering of P_{O_2} due to altitude. The difference could not be accounted for wholly by the presence of COHb. It is possible that the compensatory mechanisms normally activated by lowered P_{O_2} were not activated when CO caused the drop in O_2Hb saturation. Alternatively, it is also possible that CO exerts a specific toxic effect on the central nervous system that is unrelated to the COHb level.

In both studies just described, the investigators imply that the subjects exhibited similar responses, but they do not supply supporting data. Other investigators have commented on the great variability in response between subjects when similar tests have been used.

Lilienthal et al. (117) demonstrated an impairment in FFF in five subjects at altitudes of 3050 to 3660 m (10,000 to 12,000 ft). The combined exposure to CO (COHb increases of 5 to 9 percent) and an altitude of 1520 to 1830 m

(5000 to 6000 ft) produced an impairment in FFF test performance, although neither of these stresses alone affected it. The data indicate that an increas in the COHb level of 8 to 10 percent above resting values caused the tolerance t altitude to be lowered by 1220 m (4000 ft) or more. It should be noted that impairment in FFF performance is not necessarily consistent with a given COHb percentage. For example, at 1520 m (5000 ft) one subject showed a depressed FFF performance at 8.7 percent COHb; yet in another experiment at the same altitude, his performance remained constant at 10.5 percent COHb. There is a possiblity that COHb determinations in this experiment were inaccurate. The subjects' resting COHb levels varied from 1.0 to 3.5 percent, indicating that there were smokers in the group. Since smokers may have higher hemoglobin values than nonsmokers (118), the assumed hemoglobin value used in this experiment may not be valid.

By contrast, Vollmer et al. (119) have found that the effects of CO and altitude are not additive. Twenty subjects were used to study the effects of CO and increased altitude (3050 and 4570 m or 10,000 and 15,000 ft) on FFF, body sway, and size of the red visual field - all during light activity. Compared with performance at sea level, there was a significant impairment at increased altitude, with and without exposure to CO. There was no significant difference between the mean test scores during hypoxia alone and the mean test scores following administration of CO. The increases in COHb were from 9 to 19 percent, with a final COHb ranging from 12 to 22 percent. This suggests that the resting COHb was 3 percent, and indicates that some of the subjects were smokers. Vollmer suggests that at 4570 m (15,000 ft), any additional burden imposed by the presence of small amounts of COHb is masked by compensatory mechanisms. Alternatively, he considers that it is possible that 9 to 19 percent COHb does not impose an important additional stress. At 4720 m (15,500 ft), however, 4 of 17 subjects collapsed after being exposed to CO. The tests used in this study appear inadequate for predicting a serious cardiovascular reaction; nor can their sensitivity be ranked very high.

Most of the above studies were conducted before or during World War II. Recently, Denison (120) demonstrated a significant effect of hypoxia alone on complex reaction times at a simulated altitude of 1520 m (5000 ft) during light work. At 1520 m (5000 ft), eight of ten subjects showed slower reaction times than nine of ten matched controls ($p<0.05$). This effect of hypoxia was observed only during the early stages of learning the complex experimental task. Once the task has been learned, a simulated altitude up to 2440 m (8000 ft) had no effect. The effect of small amounts of CO on the learning of a new task at increased altitude remains to be determined.

2. Hyperbaric Conditions

Atmospheric pollution with CO in conjunction with low atmospheric pressur occurs fairly frequently; for example, in the case of airline passengers or residents of cities at high altitude. Less well recognized, though, is the constantly increasing number of persons who are subject to special hazards as a result of a combination of CO effects and elevated pressure. Oceanographic exploration and construction work performed under water, as in bridge building or tunneling, is becoming quite common. Studies are therefore being conducted both *in vitro* and *in vivo* to determine whether or not toxicity of CO exists under these conditions. Berger et al. (121) reported on studies they conducted *in vitro*, in which blood under various pressures was equilibrated with identical mixtures of CO and air. The same rate of COHb concentration was measured under various pressures at equilibrium.

Gerhardt et al. (122) worked with volunteers who were exposed to 58 and 115 mg/m^3 (50 and 100 ppm) CO under 1 and 3 atmospheres of pressure. Measurements were taken of the COHb value in the blood and of the CO concentrations in the alveolar air. They demonstrated that saturation of the blood with CO occurs much faster at higher pressure than at normal pressure, the result of an increased CO supply under increased CO partial pressure. However, the COHb concentration in the diffusion equilibrium is significantly lower at higher pressure than at normal pressure. For example, inhalation of 58 mg/m^3 (50 ppm) CO produces 4.5 percent COHb at 3 atmospheres but 7.25 percent at 1 atmosphere once a diffusion equilibrium has been obtained. By the same token, studies conducted with rabbits have proved that the CO partial pressure in the tissue as well as in the blood is lower under elevated pressure than it is under normal atmospheric pressure (97). These results can be explained by the competition of CO and O_2 for the receptor hemoglobin. This competition is governed by the law of mass action. The key factor in interpreting the above findings is that the alveolar O_2 concentration at 3 atmospheres is 19 volume-percent and is thus considerably higher than the 14.6 volume-percent at normal pressure. However, the alveolar CO concentrations are identical under both conditions.

I. ADAPTATION

A subject may be considered to be adapted (acclimatized) to a new environment when, after repeated or prolonged exposure to that environment, he shows a significant decrease in the amount of reaction experienced per unit intensity of the offending factor without an increase in other types of reaction. Adaptation thus implies some short-range benefit to the organism concerned. Individuals living at high altitude are considered to be adapted to their environment, since it has been shown that they can perform physical labor there that low-altitude residents cannot do as readily at similar elevations. High-altitude inhabitants, however, show a greater incidence of pulmonary hypertension and patent ductus arteriosis (123), both of which are associated with an increased need to maintain an adequate P_{aO_2}. Thus, not all high-altitude residents are adapted in the formal sense, but they are well compensated. Since most studies of adaptation are of brief duration, the ultimate costs in terms of parameters such as health impairment (that is, the development of pulmonary hypertension) can easily be overlooked.

Some experimental studies suggest that repeated exposures to low levels of CO result in an adaptation of the subject to additional exposures. In animal studies, the long-term exposure of dogs to low levels of CO for periods of up to 3 months (described in Section F above) has resulted in increased hematocrits, hemoglobin, and RBC counts (80). In studies of heart size after prolonged exposure to CO, cardiac enlargement has been found, presumably reflecting an increased cardiovascular work load (69). Such changes can be considered compensatory mechanisms leading to adaptation.

Astrup et al. (86) have demonstrated an increase in hemoglobin concentration in cholesterol-fed rabbits during the first 5 weeks of an 8-week exposure to 195 mg/m^3 (170 ppm) CO. The hemoglobin level then stabilized, but when the CO concentration was increased to 405 mg/m^3 (350 ppm) a further increase in hemoglobin was observed. The compensatory mechanisms that may have been responsible were not discussed by the authors. The degree of visible aortic atheromatosis and the content of total cholesterol in the aortic tissue was significantly higher in the rabbits exposed to CO than in the controls. This factor may be relevant to the pathogenesis of arteriosclerosis in man.

Wilks et al. (124) acclimatized dogs to CO doses ranging from 920 to 1150 mg/m^3 (800 to 1000 ppm). This resulted in increased RBC, hemoglobin, and blood volume. When these dogs, together with a control group of nonacclimatized dogs, were exposed to 575 mg/m^3 (550 ppm) CO for 15 hours, blood levels of COHb were the same in both groups. This suggests that at equilibrium there is no change in CO saturation with increasing hemoglobin.

Russian studies on animals in which hypoxia was created by oxygen deficiency indicate that adaptation may occur through compensation of systems other than the cardiopulmonary system (125). Such changes include increased myoglobin stores in the tissues, increased vascularization of tissues (especially brain tissue), and changes in the oxygen consumption of enzyme systems. Whether similar changes can be induced by adaptation to CO exposure remains to be determined.

Only one investigator has reported that adaptation to CO can be demonstrated experimentally in humans. Killick (126) exposed herself to 220 to 520 mg/m^3 (190 to 450 ppm) CO in air for periods of 5 to 7 hours at approximately weekly intervals for a period of 6 months. The resulting COHb level at equilibrium ranged from 16.5 percent at 255 mg/m^3 (220 ppm) CO to 39.5 percent at 460 mg/m^3 (400 ppm) CO. Carboxyhemoglobin was determined with a reversion spectroscope; this method permits subjective errors, and the COHb levels reported in this paper may be inaccurate. Carbon monoxide was measured by the iodine pentoxide method. Killick considered adaptation to have taken place when there was a diminution in symptoms with repeated exposure to the same concentration of CO;

and when there was a discrepancy between the observed COHb at the end of an exposure was less than the COHb obtained in vitro when the subject's blood was equilibrated with a mixture containing oxygen and CO at the same partial pressure as that in alveolar air. The conclusions of this study are open to question, since a basis for determining the development of adaptation was a difference between observed and calculated COHb levels. The methods used for calculation resulted in calculated arterial P_{O_2} as much as 100 mm Hg above alveolar P_{O_2}. The irregular pattern of exposure, possible erroneous calculations, and subjective methods for COHb determination render this study of limited value. In contrast to Wilks' study in dogs, however, Killick found no change in the RBC count or in the blood volume.

In summary, it can only be stated that the available data concerning physiologic adaptation of humans to CO are inconclusive. It is expected that some adaptation will take place, but the mechanism is unclear.

J. ENDOGENOUS FORMATION OF CARBON MONOXIDE

The first claims that CO could be formed within the mammalian body were reported by French investigators in the period 1898 to 1925 (127-131), but an exogenous source of CO could not be ruled out. In 1945, Roughton and Root (132) demonstrated that there was a small, but measurable, amount of CO in normal human blood. In 1949, Sjostrand (133) observed that the expired air of human subjects who were not exposed to exogenous CO contained consistently more CO than the inspired air, suggesting that CO was being produced in the body. Sjostrand's findings were confirmed by Coburn et al. (134), who with the use of a sensitive analytical method for blood CO were able to measure directly the rate of CO formation by using a rebreathing system. The average rate of CO production in man was found by Coburn et al. to be 0.42 ± 0.07 ml per hour, which is slightly lower than Sjostrand's value of 0.5 to 1.0 ml per hour in the normal adult female.

Utilizing a rebreathing system and the Haldane equation, Sjostrand estimated an indirect value for COHb from the rebreathing gas samples at the end of the rebreathing period (41). Both Sjostrand (135) and Engstedt (136) have noted that the COHb level thus calculated is positively correlated with the presence of hemolytic disease or other states associated with increased hemoglobin breakdown, such as extensive trauma or mismatched transfusions (137,138). These findings have been more precisely confirmed by Coburn et al. (134,139) with their improved analytical techniques.

Sjostrand (140) has also demonstrated that solutions of hemoglobin and myoglobin liberate CO upon standing, and that maximal production of CO from such solutions corresponds to the CO-binding capacity of the initial solution. Injections of hemolyzed blood and hemoglobin solutions into humans, dogs, and rabbits have been observed to cause an increased endogenous production of CO (141,142). By injecting damaged erythrocytes, Coburn et al. (139) have demonstrated a molar ratio between the amount of heme destroyed and the amount of CO formed. The increase in CO formation occurs simultaneously with rising levels of serum bilirubin, a metabolic product of hemoglobin.

The experimental data indicate that endogenous CO is a by-product of heme catabolism. In vivo, the end products of hemoglobin catabolism are the bile pigments, which arise specifically from the heme group of the hemoglobin. Heme, which is a cyclic tetrapyrrole, loses its α-methene-bridge carbon atom to form bilirubin, which is linear tetrapyrrole. Libowitzky and Fischer (143) have been unable to recover this missing one-carbon fragment in vitro as either formic acid or formaldehyde. Sjostrand (140-142) has suggested that the missing carbon atom is incompletely oxidized to CO, which is then excreted in the expired air. Ludwig et al. (144) have confirmed this suggestion by using ^{14}C-labeled heme.

Other heme-containing proteins are also likely sources of endogenous CO, provided the initial steps of their catabolism are similar to those of hemoglobin. It is known that approximately 10 to 15 percent of the total bile pigment production comes from sources other than circulating red cell hemoglobin. These sources (145) may be:

1. Myoglobin heme catabolism.
2. Catabolism of heme-containing enzymes (cytochromes, catalases, etc.).
3. Excess production of heme in marrow and other sites.
4. Production of bilirubin through anabolic pathways.
5. Early death of red blood cells within the marrow or shortly after their release (ineffective erythropoiesis).
6. A scarf of hemoglobin around the extruded nucleus of the normoblast.

In their radioactive tracer studies, White et al. (146) have demonstrated that labeled CO was produced within the first few days following injection of glycine-2-^{14}C. This radioactive amino acid specifically labels the α-methene-bridge carbon atom of heme. The amount of labeled CO recovered was of the correct order of magnitude to account for the excess CO. Similar results have been reported in studies of heme catabolism in rodents (147). In addition, White et al. (148) have demonstrated the production of CO from liver slices in vitro, with the simultaneous production of bilirubin. This has confirmed earlier studies (149,150), demonstrating that nonhemoglobin hemes in the liver are important sources of bile pigment.

Schwartz et al. (151), using hypertransfused mice in which erythropoiesis was nearly 100 percent suppressed, have estimated that about 40 percent of the early appearing bile pigment (and CO) came from the catabolism of non-hemoglobin hemes. Recently, direct evidence of increased CO production in states associated with increased ineffective erythropoiesis has been obtained (152).

An appreciation of the importance of endogenously produced CO in clinical and experimental conditions is developing. It has been noted that patients presumably not exposed to CO do, when undergoing anesthesia, produce CO levels within rebreathing anesthesia apparatus; these CO concentrations often exceed 58 to 115 mg/m^3 (50 to 100 ppm) (153). This concentration exceeds the maximum allowable levels for industrial workers who are exposed to CO for 8 hours. It has been suggested that these closed rebreathing systems be opened and flushed periodically during the operative procedure in order to remove the excess CO. Some of this increase in CO during anesthesia may be due to the increased oxygen tension of inspired air, which, according to the Haldane equation will promote the dissociation of COHb (154,155). Increased COHb levels are also seen in newborn infants (154,155), because of both normal and abnormal hemolysis. The endogenous production of CO in the newborn leads to increased COHb levels (up to 12 percent) and results in relative impairment of oxygen transport function.

It has long been known that CO arising from internal combustion engines, tobacco smoke, and other conventional sources in submarines is an important cause of atmospheric pollution in the crew's quarters. In other closed systems containing men or animals, the puzzling production of CO has been noted. Toxic or fatal CO levels have even occurred in some animal experiment when the contaminant was not specifically removed. It is implied that the crew members (or the experimental animals) themselves are an important source of CO pollution in closed systems. Greater attention is now being focused on the endogenous production of CO in closed systems that are being evaluated for use in space flights and undersea exploration.

It is conceivable that animal-plant cycles proposed for long space flights as oxygen producers and waste-product removers may themselves turn out to be an additional source of CO. This could result from the decomposition of chlorophyll, the green pigment of plants, which contains a cyclic tetrapyrrole structure similar to heme. Mature leaves have been shown to produce large quantities of CO, presumably from degradation of chlorophyll (156).

There is the possibility that a CO cycle exists in nature, since it has been demonstrated that many animal and plant species produce this compound (156-160). Carbon monoxide can also be utilized for metabolic purposes in certain bacteria (161) and plants (162), and may even be oxidized to CO_2 at low rates in animals (163) and in man (99). A discussion of possible biological sources of CO appears in Chapter 1 of this report.

K. SUMMARY

Carbon monoxide is absorbed exclusively via the lungs, and most of its toxic properties are a result of its reaction with hemoproteins. The primary effect of CO is mediated by its reaction with hemoglobin to form carboxyhemoglobin (COHb), thus reducing the oxygen-carrying capacity of the blood and accounting for about 80 percent of an inhaled dose of CO. The affinity of hemoglobin for CO is more than 200 times that for oxygen, indicating that COHb more stable than oxyhemoglobin (O_2Hb). The presence of COHb also shifts the O_2Hb dissociation curve to the left, implying that, at the tissue level of the circulation, less oxygen is available to the cells because of the decrease in oxygen tension (P_{O_2}). About 20 percent of a given dose of CO passes from the intravascular to the extravascular pool, reacting primarily with myoglobin to form carboxymyoglobin (COMb). About 1 percent or less reacts with the heme-containing cytochromes, and, at CO concentrations commonly encountered in community air pollution, this reaction is unlikely to be of any physiological significance.

The most accurate analysis of relatively low blood COHb concentrations results from determination of the CO liberated from the blood when the hemoglobin is destroyed. The necessary equipment is quite costly, a tedious procedure is involved, and relatively large blood samples are required. Several other good methods exist for the determination of low blood CO levels. The normal "background" concentration of blood COHb is about 0.5 percent, and this is attributed to endogenous sources such as heme catabolism. The body uptake of exogenous CO is determined by the concentration, length of exposure, and ventilatory rate, as well as by many other factors. When the concentration remains constant, a state of equilibrium is reached in which the partial pressure of CO (P_{CO}) in the pulmonary capillary blood is almost equal to that in the alveolar and ambient air. The rate of uptake of CO is fairly constant with respect to blood COHb until about one-third of the equilibrium value is reached, and then this uptake proceeds at a slower and slower pace. COHb concentration at equilibrium is about 0.16 times the exposure level of CO in ppm A reliable mathematical model exists for predicting COHb levels under a variety of circumstances.

The observed toxic effects of CO in both animals and humans reflect the impairment of the oxygen transport system. The data on experimental exposures of animals and humans are shown in Tables 7-11 and 7-12.

Table 7-11. SUMMARY OF EFFECTS OF CARBON MONOXIDE IN ANIMALS

Species	CO level	Length of exposure	COHb, %	Effect	Reference
Dogs	58 mg/m^3 (50 ppm)	6 hrs/day, 5 days/wk, for 6 wk 24 hr/day, 7 days/wk, for 6 wk	2.6 to 5.5	Brain: Mobilization of glia and dilatation of lateral ventricles. Necrosis and dilineation absent. Heart: 10/15 developed EKG changes in third week.	Lindenberg et al. (57)
Rats Rabbits Dogs	58 mg/m^3 (50 ppm)	24 hr/day, 7 days/wk, for 3 mo	Rats 1.8 Rabbits 3.2 Dogs 7.3	Dogs: No changes in EKG's and pulse rates. No histologic difference between exposed and control animals. Significant increases in hemoglobin levels, hematocrits, and RBC counts.	Musselman et al. (81)
Rats	58 mg/m^3 (50 ppm)	24 hr/day, 7 days/wk, for 3 mo		EKG changes in the first 2 weeks returning to normal in third week. Slight increase in hemoglobin levels, hematocrits, and RBC counts.	Roussel et al. (82)
Rats	58 mg/m^3 (50 ppm)	1 hr 1 to 5 hr/day for 4 days		Changes in EEG increasing in severity with length of exposure. Progressive deterioration in EEG returning to normal 48 hours after end of exposure.	Xintaras et al. (59)
Dogs	115 mg/m^3 (100 ppm)	6 hr/day, 5 days/wk, for 6 wk 24 hr/day, 7 days/wk, for 6 wk	7 to 12	Brain: Mobilization of glia and dilatation of lateral ventricles. Necrosis and demyelination absent. Heart: 8/8 developed abnormal EKG's after about 2 weeks. Autopsy: dilatation of right heart and occasionally of left heart; some degeneration of heart muscle.	Lindenberg et al. (57)
Dogs	115 mg/m^3 (100 ppm)	5-3/4 hr/day, 6 days/wk, for 11 wk	up to 21	Brain: No changes in EEG or in peripheral nerves. Consistent disturbance of postural reflexes and gait. Autopsy: 6/6 showed some indication of cortical damage. Heart: 1/4 had inverted T-wave after second week 2/4 had inverted T-wave by tenth week Autopsy: 4/4 showed degenerative changes in muscle fibers.	Lewey and Drabkin (56)

Table 7-11 (continued). SUMMARY OF EFFECTS OF CARBON MONOXIDE IN ANIMALS

Species	CO level	Length of exposure	COHb, %	Effect	Reference
Rats	115 to 11,500 mg/m^3 (100 to 10,000 ppm)	up to 48 min.	n.a.	Impairment in time discrimination.	Beard and Wertheim (58)
Rabbits	195 mg/m^3 (170 ppm)	8 weeks	19.7 at end of first week	Decrease in % COHb from 19.7 to 15.1. Increase in hemoglobin level in first five weeks followed by stabilization. Exposure to 400 mg/m^3 (350 ppm) caused further increase in Hb. Rats were cholesterol fed. Increased total cholesterol in aortic tissue in rabbits exposed to CO.	Astrup et al. (86)
Dogs	920 to 1150 mg/m^3 (800 to 1000 ppm)	6 to 8 hr/day, 7 days/wk, for 36 wks		Increased RBC counts, hemoglobin, and blood volume. Challenge with 575 mg/m^3 (500 ppm) in these dogs produced the same % COHb as in non-acclimatized controls.	Wilks et al. (124)
Dogs	>1,150 mg/m^3 (1,000 ppm)	n.a.	3 to 40	Prominent EKG changes. High mortality rate. Alterations in cerebral and myocardial histology.	Preziosi (83)
Dogs	115 mg/m^3 (100 ppm)	6 wk, continuous and intermittent	7 to 12	EKG changes, more marked with continuous than intermittent exposure. Dilatation of right cardiac chamber. Dilatation of lateral ventricles of the brain.	Preziosi (83)
	58 mg/m^3 (50 ppm)	6 wks, continuous and intermittent	2.6 to 5.5	Same changes as noted with exposure to 115 mg/m^3, except EKG changes were not as prominent.	
Mice	58 mg/m^3 (50 ppm)	3 mo to 2 yr	n.a.	No changes noted in fertility, fetal survival, body growth, food intake, weight and water content of various organs, EKG, or blood chemistries.	Stupfel (61)
Monkeys	55 mg/m^3 (48 ppm)	n.a.	3.7 to 4.7	No decrement in performance, even at simulated altitude of 27,000 feet.	Back and Dominguez (62)

Table 7-12. SUMMARY OF EFFECTS OF CARBON MONOXIDE IN HUMANS

No. Subjects	CO level	Length of exposure	COHb, %	Effect	Reference
7	115 to 23,000 mg/m^3 (100 to 20,000 ppm)	Up to 5 hr	Up to 35.0	Uptake of CO increases with concentration of CO, length of exposure and ventilation rate. Rate of uptake of CO as measured by increase in blood % COHb is constant up to 1/3 of equilibrium COHb. Rate of uptake decreases with increased P_{O_2} and apparently increases with decreased P_{O_2} due to hyperventilation. When the latter is corrected for, rate of uptake is unaltered.	Forbes et al. (44)
10	35 mg/m^3 (30 ppm)	24 hr	5	Approximate equilibrium value of COHb reached by 12 hours; 60% of equilibrium value reached in 2 hours, 80% in 4 hours, and the remainder over 8 hours.	Smith (47)
4	100% (100 to 300 ml)	10 to 15 min	Up to 20	Impairment of visual function detectable at approximately 4.5% COHb and increases with increase in COHb. Recovery lags behind excretion of CO. Latter depends on composition of gas during post-exposure period. Experiments at simulated altitudes gave a similar pattern of results. Data given for one subject only.	Halperin et al. (116)
1	n.a. (1 cigarette)	n.a.	2	Impairment of visual function.	MacFarland et al. (74)
1	n.a. (3 cigarettes)	n.a.	4	Impairment of visual function similar to that produced by an altitude of 8000 ft.	
49	n.a.	n.a.	Up to 20.4	Impairment in response to certain psychomotor tests, detectable at 5% COHb. No effect on pulse, respiratory rate, blood pressure, neurological reflexes, muscle persistence, or static steadiness test.	Schulte (64)

Table 7-12.(continued.) SUMMARY OF EFFECTS OF CARBON MONOXIDE IN HUMANS

No. Subjects	CO level	Length of exposure	COHb, %	Effect	Reference
18	58 to 230 mg/m^3 (50 to 250 ppm)	Up to 2 hr	2.5	Significant impairment in time-interval discrimination after exposure to 58 mg/m^3 (50 ppm) for 90 minutes	Beard and Wertheim (58)
4	58 to 230 mg/m^3 (50 to 250 ppm)	Up to 2 hr	3	Consistent impairment in 3 or 4 parameters of visual function after exposure to 58 mg/m^3 for 50 minutes.	Beard and Grandstaff (70)
18	29 to 1,150 mg/m^3 (25 to 1000 ppm)	Up to 16 hr	Up to 31.8	No impairment of time estimation. No change in blood chemistry.	Stewart et al. (66)
	Up to 115 mg/m^3 (100 ppm)	8 hr	11 to 13	No impairment in psychomotor test performance.	
42	115 mg/m^3 (100 ppm)	3 1/2 hr	7.2	Impairment of visual perception, of manual dexterity, of learning, and impairment of performance of certain intellectual tasks.	Bender et al. (71)
20	58, 115, and 174 mg/m^3 (50, 100, and 150 ppm)	110 min	not measured	Impairment of auditory vigilance: percentage of missed signals is correlated to CO concentration in inspired air. Impairment of EEG.	Groll-Knapp (72)
12	58 mg/m^3 (50 ppm)	5 hr	not measured	Impairment of auditory vigilance between the 80th and 125th min of exposure. No changes in psychomotor tests.	Fodor and Winneke (73)
5	n.a.	Up to 2 min	Above 5	Decreased P_{aO_2} and P_{vO_2}.	Ayres et al. (91)
26	n.a.	Up to 2 min	Above 5 (average 8.96)	Increased oxygen extraction in the presence of COHb.	Ayres et al. (92)
111	n.a.	Up to 2 min	Above 5 (average 8.5 to 9)	Increased lactate production in patients with coronary heart disease; increased coronary blood flow, and fall in mixed venous and coronary sinus P_{O_2}.	

Studies have shown that the long-term exposure of animals to CO may produce morphological changes in the heart and brain. Dogs exposed intermittently or continuously to 58 mg/m^3 (50 ppm) for 6 weeks developed abnormal EKG's after the third week. At autopsy, these same dogs showed mobilization of glia and dilatation of the lateral ventricles of the brain. Continuous exposure of dogs to 58 mg/m^3 for 3 months failed to show such changes, but significant increases in hemoglobin levels, hematocrits, and RBC counts were observed. Continuous and intermittent exposure of dogs to 115 mg/m^3 (100 ppm) for 6 weeks produced a dilatation of the chambers of the right heart and, occasionally, of the left heart, and some degeneration of heart muscle was also noted. Dogs exposed to 115 mg/m^3 for 5-3/4 hours a day, 6 days a week for 11 weeks developed a consistent disturbance of the postural reflexes and of gait, although no changes in the electroencephalogram (EEG) or the peripheral nerves were reported. At autopsy, there was some indication of cortical damage.

The effects of CO on the hematological system of animals suggest the possibility of adaptation to CO. Cholesterol-fed rabbits that were adapted (acclimatized) by exposure to 195 mg/m^3 (170 ppm) CO for 8 weeks showed an increase in the hemoglobin level during the first 5 weeks of exposure; the level stabilized during the following 3 weeks. When the CO concentration was increased to 405 mg/m^3 (350 ppm), a further increase in hemoglobin was observed.

In other studies, short-term exposure of animals to low levels of CO produced effects on the central nervous system. Rats exposed to 58 mg/m^3 (50 ppm) for 1 hour developed alterations in the electroencephalogram (EEG), which increased in severity with longer periods of exposure. These changes returned to normal 48 hours after the end of the exposure. After exposure to 58 mg/m^3 for 48 minutes, rats developed an impairment in time discrimination. Short-term exposure to higher CO concentrations produced similar effects, but with increased severity.

No long-term human studies on experimental CO exposures have been reported, although there are data on occupational exposures. Brief exposures to high levels of CO produced effects on the central nervous, vascular, and respiratory systems. Central nervous system effects apparently occurred at COHb levels above 2 percent. Exposure of nonsmokers to 58 to 290 mg/m^3 (50 to 250 ppm) CO for up to 2 hours produced a significant impairment in time discrimination, statistically significant at about 58 mg/m^3 for 90 minutes (approximately 2.5 percent COHb). At blood COHb levels of about 3 percent (estimated by expired air analysis after exposure to 58 mg/m^3 of CO for 50 minutes), significant changes in relative brightness threshold and visual acuity were observed. Impairment in the performance of certain psychomotor tests occurred at about 5 percent COHb. Exposure of four subjects to 100 to 300 ml of pure CO for several minutes produced an impairment in visual function, which was significant when the blood COHb level in one subject reached about 4.5 percent.

Exposure to CO affects oxidative metabolism of both systemic and myocardial circulatory beds. Blood COHb levels above 5 percent in five subjects produced a mean decrease of 13.3 percent in mixed venous oxygen tension and 7.3 percent in arterial oxygen tension. In 26 subjects whose mean COHb was 8.9 percent, there was a mean decrease in the venous P_{O_2} that could be correlated with an increase in COHb. There were also associated increases in oxygen extraction ratios, ventilation, and cardiac output.

Myocardial metabolic studies have demonstrated that concentrations of CO sufficient to produce significant increases in COHb may produce a severe burden in subjects who already have increased demands on their oxygen supply, such as persons with coronary artery disease. Eleven cardiac patients, four of whom had coronary artery disease, were exposed to CO that produced a mean COHb level of almost 9 percent, with several patients having blood COHb levels in the range of 5.5 to 6.5 percent. Patients with noncoronary heart disease showed a compensatory increase in coronary blood flow in response to the increased myocardial oxygen needs; this response did not occur in the four patients with coronary heart disease. In addition, the inadequate oxygen supply to the myocardium was reflected in the lactate extraction ratio, which changed to production in these four patients. It thus appears that people with certain forms of heart disease may be particularly susceptible to exposures of CO that could lead to blood COHb levels in excess of 5 percent. Many people with preclinical coronary artery disease may also have diminished myocardial performance at these levels.

The effects of CO are especially important at high altitude because of the lowered P_{O_2}. Both physiological and psychomotor tests have been employed to demonstrate these effects. As indicated by the increase in exercise pulse rate, each increase of blood COHb of 1 percent, up to 13 percent, has been shown to be equal in effect to about 100 m (335 ft) of altitude, applied over the altitude range of 2130 to 3050 m (7,000 to 10,000 ft). Impairment of visual threshold perception in a single subject at 2130 m (7000 ft) was equivalent to that produced by 5 percent COHb at sea level. In five subjects, a COHb level of 8 to 10 percent has produced a mean impairment in flicker fusion frequency (FFF) that was equivalent to lowering the altitude tolerance 1220 m (4000 ft) from about 3050 to 1830 m (10,000 to 6,000 ft).

In many of the human studies, the brief exposures to very high levels of CO make it difficult to relate the observed effects to equilibrium COHb levels. For long-term exposure to CO, certain effects such as increased hematocrits, hemoglobin levels, and blood volume may be present, but the available data are inadequate for drawing firm conclusions concerning the significance of all of these changes.

In summary, appraisal of short-term experimental exposures of humans to CO shows the following results in terms of the blood COHb levels observed:

1. No human health effects have been demonstrated nor have they been observed for COHb levels of 0 to 1 percent, since endogenous CO production makes this a physiological range.
2. The following effects on the central nervous system have been observed at 2 to 5 percent COHb:
   a. At an estimated level of about 2.5 percent COHb in nonsmokers (based on exposure to 58 mg/m^3 CO for 90 minutes), an impairment in time-interval discrimination has been demonstrated.
   b. At COHb levels of about 3 percent (based on exposure to 58 mg/m^3 for 50 minutes), changes in visual acuity and relative brightness threshold have been documented.
   c. At about 5 percent COHb, an impairment in the performance of certain other psychomotor tests, and an impairment in visual discrimination, have been demonstrated.
3. The following cardiovascular changes have been observed at COHb levels of 5 to 10 percent:

a. In patients without coronary heart disease, changes were noted in cardiac output, (increased), systemic arterio-venous oxygen-content difference, systemic oxygen extraction ratios, myocardial arterio-venous oxygen-content difference, and coronary blood flow.

b. In patients with coronary heart disease, lactate extraction changes to production and the compensatory increase in coronary blood flow is absent.

c. In patients with preclinical coronary artery disease, abnormal EKG's may increase.

Long-term experimental exposure of humans to CO may produce certain adaptive effects such as increased hemoglobin and hematocrits, but the available data are inadequate for drawing firm conclusions. Such effects have been observed in animals. There is a definite need to evaluate further the effects of cigarette smoking on the central nervous and cardiovascular systems, and to evaluate as well the possible "adaptation" of the cigarette smoker to CO.

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CHAPTER 8.

EPIDEMIOLOGICAL APPRAISAL OF CARBON MONOXIDE

A. INTRODUCTION

Studies to determine the effects of CO upon health have usually involved short-term high-concentration exposures to CO; therefore, the observed clinical effects are often attributable to hypoxia. Many of these effects are considered to be reversible as CO is eliminated from the body (1,2). A number of recent clinical and laboratory studies have resulted in the concern that subtle cardiovascular and central nervous system effects may be associated with elevated CO levels in the atmosphere.

Epidemiologic studies, as distinguished from toxicologic or experimental studies, deal with the effects of pollution in the ambient air on groups of people living or working in a community or area. In such studies, health effects are examined as they occur naturally, rather than in a laboratory; but this type of study also has the disadvantage that all the factors of possible importance cannot be controlled. Nevertheless, the preparation of air quality criteria should include both epidemiologic studies and laboratory studies.

In air pollution epidemiology, gross mortality data have been an insensitive way of measuring health effects. Further, there is often inappropriate designations of cause of death or variations in certification of cause of death, and there is usually a lack of autopsy data. Systematic study of morbidity associated with exposure to CO is handicapped by this lack of available indices of health effects.

Hospital admissions data are one form of useful information, but problems caused by variability in availability of beds, day-of-week biases, changing medical staff, overtime, and altered criteria for admission make this information susceptible to misinterpretation. Some of these problems have been dealt with by Sterling et al. (3,4) in a study utilizing Blue Cross (prepaid hospitalization insurance) hospital admission data as an index of morbidity.

The problems of associating monitoring station data with the actual impact on the individual who is exposed to a number of environments during the course of a day has been dealt with by Goldsmith et al. (5). Because of the relative ease in determining carboxyhemoglobin (COHb) levels by the analysis of expired air, the potential for using each individual as his own monitoring system should be considered in many cases (6). In several occupational studies, COHb levels have been measured in individuals exposed to high concentrations of CO and attempts have been made to relate COHb levels to health effects. These studies are discussed in the following sections.

B. SOURCES AND MAGNITUDE OF EXPOSURE TO CARBON MONOXIDE

The numerous sources of CO and their relative contributions to body COHb levels are just beginning to be assessed. In addition to the CO encountered in community air, man is personally exposed to individual sources such as cigarette smoke, household heaters, cooking fumes, and occupational pollution. Detecting and estimating the contribution of community air pollution in the presence of multiple exposures poses a complex problem. Fortunately, it is easy to estimate the amount of CO in the body by expired air analysis after 20-second breathholding (7-9). (Limitations in the application of this method to nonsmokers are discussed in Chapter 7, Section C.3 of this report.)

1. Community and Residential Exposures

Because of the large number of motor vehicles in operation, CO is produced in sufficiently large quantities in certain cities that it can no longer be considered a problem only in the immediate vicinity of traffic; it may now be found throughout entire communities (10,11). (Quantitative discussion on the extent of this problem is given in Chapters 3 and 5 in this report.)

Haagen-Smit has measured the CO levels to which the commuter is exposed in Los Angeles city traffic (12). He found that the average concentration was 43 mg/m^3 (37 ppm) CO and that this level increased to 62 mg/m^3 (54 ppm) in slow and heavy traffic.

Goldsmith et al. (5,8) have reported on the increase in COHb in two pairs of subjects - a smoker and a nonsmoker in each pair - exposed together to Los Angeles conditions. Some results of this work are shown in Figures 8-1 and 8-2.

A theoretical approach has been postulated for estimating effects of population exposure to CO by inference from an exposure pattern and indirect measurement of the mean COHb levels in the population. The application of such a procedure would be more valid than current methods of environmental surveillance.

A recent review describes several household sources of CO (13). In addition, it has also been shown that open fires and charcoal braziers produce a substantial amount of CO (14). A field study in New Guinea also indicates that high levels of CO may be present in native huts when cooking is done (15). Some of the seasonal variations reported for COHb concentrations in individuals

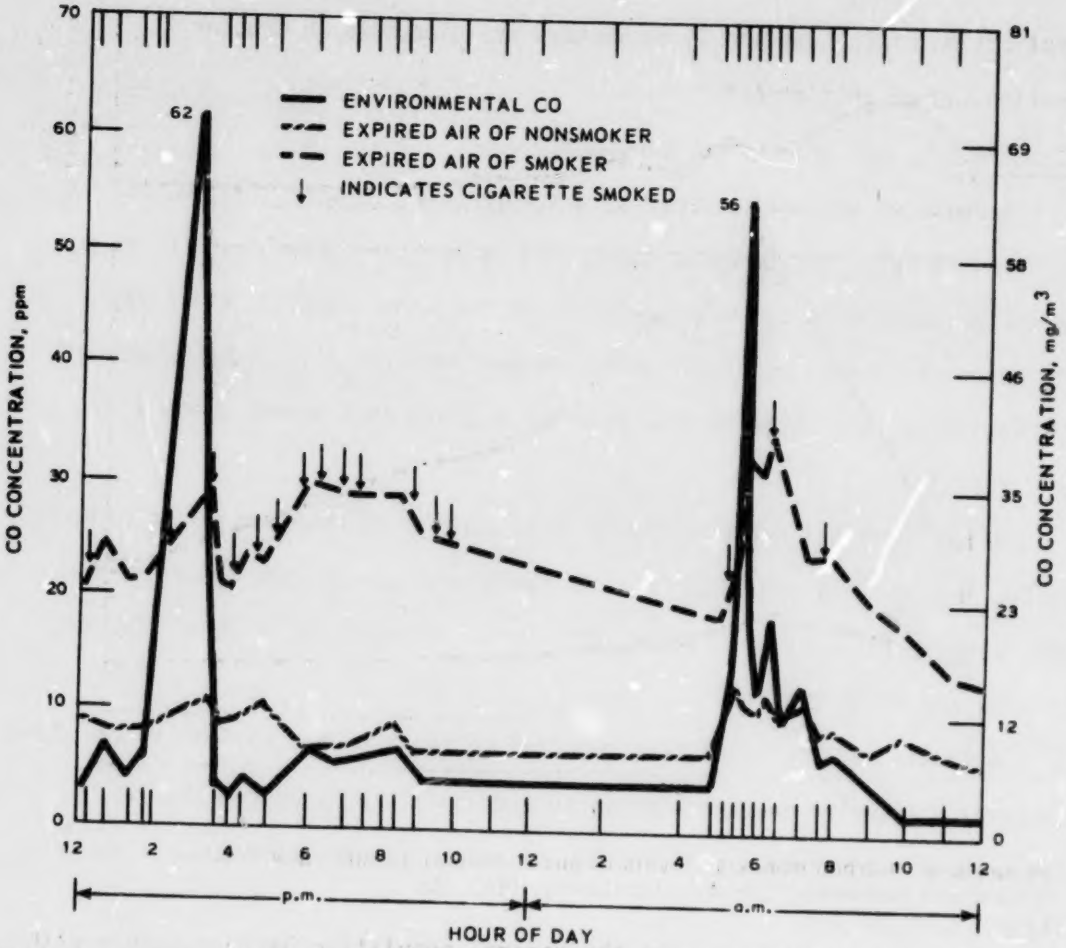

Figure 8-1. Carbon monoxide levels of environmental air and of expired air of smoker and nonsmoker, Los Angeles and Pasadena, August 1962 (5).

may be attributable to household heating. A further discussion of levels of CO measured in households appears in Chapter 5, Section D of this report.

Community CO levels have been monitored in a variety of areas to determine the distribution and magnitude of exposure. Very little attention, however, has been directed toward the influence of community exposure upon household CO levels.

2. Occupational Exposures

Most epidemiologic studies of the effects of CO on human health have dealt with occupationally exposed groups. These studies cannot be

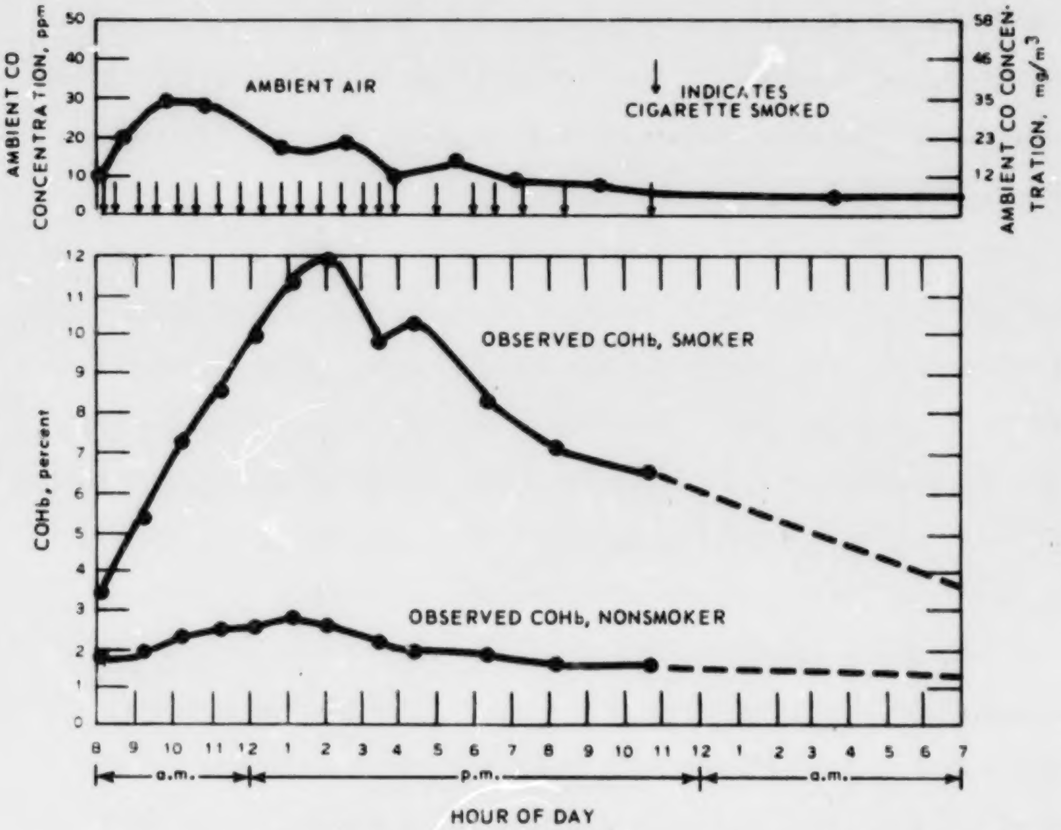

Figure 8-2. Carbon monoxide levels of environmental air and carboxyhemoglobin levels of smoker and nonsmoker, Los Angeles County, 1963 (8).

extrapolated quantitatively to the general population because people with severe anemia, cardiovascular insufficiency, or other debilitating conditions are unlikely to be working in places such as traffic tunnels, steel mills, or parking garages. In addition, people occupationally exposed to CO may simultaneously be exposed to a number of other environmental sources of CO, and the contribution of each possible source may be difficult to isolate. The effects usually observed in occupational studies of CO are increased levels of COHb and the disputed "chronic carbon monoxide poisoning syndrome," (16,17) which consists of recurrent symptoms such as headache, dizziness, exertional dyspnea, diarrhea, urinary frequency, sweating, thirst, weight loss, loss of libido, and insomnia.

Grut (16) studied drivers of vehicles propelled with "producer gas" in Copenhagen during World War II. He indicated that 46 percent of 721 drivers had chronic CO poisoning, characterized by fatigue, headache, irritability, dizziness, and disturbed sleep.

Lindgren (17) examined two similar groups of workmen, one of which was occupationally exposed to CO. The exposed group, with significantly higher COHb levels, included 970 subjects; the control group included 432 subjects. He found no higher frequency of symptoms and signs typical of chronic CO poisoning in the exposed group than in the control group. He also found no differences in the frequency of illness between the two groups, based on national health insurance records over a period of 10 years.

An important study of occupational exposure to CO was conducted among employees of New York's Holland Tunnel (18,19). The average exposure through all parts of the tunnel throughout the day was estimated to be 80 mg/m^3 (70 ppm), with peak concentrations rarely higher than 230 mg/m^3 (200 ppm). The levels of CO found in the blood of traffic officers stationed in the tunnel for a 2-hour period were within the range usually observed in cigarette smokers with no occupational exposure to CO. In addition, the amounts of CO absorbed during tunnel duty appeared to add to amounts acquired from cigarette smoking. No complaints attributable to CO exposure were noted. Hemoglobin determinations were reported as normal for all exposed individuals. Urinalysis did not reveal abnormalities of glucose or albumin.

Hofreuter et al. (20) studied 68 employees of a vehicle inspection center where hourly CO concentrations averaged 58 mg/m^3 (50 ppm), with these measurements ranging from 12 to 173 mg/m^3 (10 to 150 ppm). The average blood COHb level for this exposed group was 3.74 percent; this was significantly higher ($p<0.01$) than the average of 2.67 percent COHb found in a control group. Average hemoglobin levels were also significantly higher in the exposed group. The high average COHb level in the control group is attributed to the majority of subjects in each group being smokers.

Ramsey (21) studied 38 parking garage employees whose occupational exposure to CO averaged 68 mg/m^3 (59 ppm) during the work day. Carboxyhemoglobin levels in these individuals were significantly different from those in a control group not exposed to motor vehicle exhaust. Their hemoglobin levels were also significantly higher than those of control subjects. Ramsey thought that occupational exposure appeared to be more important than smoking in determining COHb levels in this group (Table 8-1).

Table 8-1. COHb LEVELS OF SMOKERS AND NONSMOKERS IN EXPOSED AND CONTROL GROUPS (21)

Group		COHb, %			
		a.m.		p.m.	
		Mean	S D	Mean	S D
Exposed (parking garage)					
Nonsmokers	14	1.5	±0.83	7.3	±3.46
Smokers	24	2.9	±1.88	9.3	±3.16
Controls					
Nonsmokers	10	...	....	0.81	±0.54
Smokers	17	...	....	3.9	±1.48

de Bruin (22) measured COHb levels of policemen and drivers in Rotterdam and Amsterdam. Blood samples obtained before and after work showed increased COHb in those occupationally exposed. A control group showed no such increase.

Cohen et al. (23) studied carbon monoxide uptake by inspectors at a United States-Mexico border station. Hourly ambient CO levels ranged from 5.75 to 195.5 mg/m^3 (5.0 to 170.0 ppm) during the three shifts. The average hourly CO concentration was 15.8 mg/m^3 (13.8 ppm) during the 8 a.m. to 4 p.m. shift, 75.4 mg/m^3 (65.6 ppm) during the 4 p.m. to midnight shift, and 131.5 mg/m^3 (114.4 ppm) during the midnight to 8 a.m. shift. When nonsmoking, exposed individuals on all shifts combined were examined (Table 8-2), the differences between before and after work expired-air CO values were statistically significant. According to the relationship between

Table 8-2. CHANGE IN EXPIRED-AIR CARBON MONOXIDE LEVELS DURING WORK IN EXPOSED AND CONTROL BORDER EMPLOYEES (23)

		Before Work			After Work			
	No. of Subjects	Mean Expired Air CO (ppm)	SE	Calculated Mean COHb %	Mean Expired Air CO (ppm)	SE	Calculated Mean COHb %	Change in Expired Air CO During Work Shifts
				All Shifts				
Exposed								
Nonsmokers	9	5.7	1.05	1.5	18.6	2.27	3.6	Increased*
Smokers	11	25.5	4.01	4.8	35.0	4.53	6.4	Increased†
Controls								
Nonsmokers	5	8.2	2.42	1.9	5.4	1.25	1.4	Decreased
Smokers	1	41.0	...	7.4	41.0	...	7.4	No change
				4 PM-Midnight and Midnight-8 AM Shifts Only				
Exposed								
Nonsmokers	7	5.0	0.90	1.4	21.0	3.70	4.0	Increased*
Smokers	6	19.2	2.34	3.8	[illegible]	6.77	7.6	Increased†
Controls								
Nonsmokers	2	4.3	1.00	1.1	3.5	0.50	1.0	Decreased
Smokers	1	41.0	...	7.4	41.0	...	7.4	No change

* P < 0.01.
† P < 0.02.

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COHb and expired-air CO, this represented 1.5 percent COHb before duty and 3.6 percent COHb after duty. Smoking, exposed individuals on all shifts combined did not have significant differences between before and after work expired-air CO levels. The CO values noted corresponded to 4.8 percent COHb prior to duty and 6.4 percent COHb after duty. An examination of ambient CO levels indicated that these levels were considerably lower during the first work shift. Therefore, there is some justification for examining separately the data obtained during the two shifts when high ambient CO levels occurred. When this was done, the difference in the mean expired-air CO of exposed nonsmokers remained statistically significant, and smokers had an increase in expired-air CO during the work shift that also is highly significant (Table 8-2). Control smokers and nonsmokers continued to have no significant change in CO uptake. The data from the last two shifts showed that the change in the mean COHb level during the work period was +2.6 percent COHb for nonsmokers and +3.8 percent COHb for smokers. The similarity in the increments in COHb in nonsmokers and smokers suggested that approximately the same amount of CO was absorbed by both during the period of exposure. Because smokers started with much more CO already present in their blood, the proportional increase was less and became more difficult to detect with the statistical method used.

Clayton et al. (24) found increases in COHb levels in smoking (3.1 to 3.9 percent COHb) and nonsmoking (0.8 to 1.2 percent COHb) subjects travelling in a police scout car for 8 hours in traffic; the average CO level measured during this period was 20 mg/m^3 (17 ppm), although a peak of 138 mg/m^3 (120 ppm) was recorded. After also studying the COHb levels of 237 individuals involved in traffic accidents, these authors concluded that the CO level in the Detroit urban area does not appear to be related to impaired driving ability. It is interesting to note that the information presented in Table 8-3 and Figure 8-3 shows that drivers involved in accidents had higher COHb levels than pedestrians did, though the differences are not statistically significant. No attempt was made to relate accident rate to ambient CO level in this study. The implications of the possible relationship between ambient levels of CO, blood COHb levels, and the occurrence of motor vehicle accidents suggest that this is an important area for future research.

Table 8-3. FREQUENCY DISTRIBUTION OF CO BLOOD ANALYSES OF INDIVIDUALS INVOLVED IN TRAFFIC ACCIDENTS (24)

COHb, %	Total number of analyses (cumulative percent in parentheses)		Status of individuals involved[a]			
			Drivers	Pedestrians	Passengers	Status unknown
1.0	73	(32.2)	27	30	5	11
1.0- 1.9	45	(52.0)	21	17	1	6
2.0- 2.9	30	(65.2)	14	11	1	4
3.0- 3.9	14	(71.4)	6	6	-	2
4.0- 4.9	25	(82.4)	12	6	3	4
5.0- 5.9	14	(88.5)	6	7	-	1
6.0- 6.9	10	(93.0)	3	4	1	2
7.0- 7.9	7	(96.0)	5	2	-	-
8.0- 8.9	4	(98.0)	3	1	-	-
9.0- 9.9	2	(98.7)	2	-	-	-
10.0-10.9	1	(99.1)	-	-	-	1
11.0-11.9	1	(99.6)	1	-	-	-
31.5	1	(100)	-	-	-	1
Clotted	7		2	3	1	1
Broken	3		1	2	-	-
Totals	237		103	89	12	33

[a]The difference in COHb between drivers and pedestrians is not statistically significant.

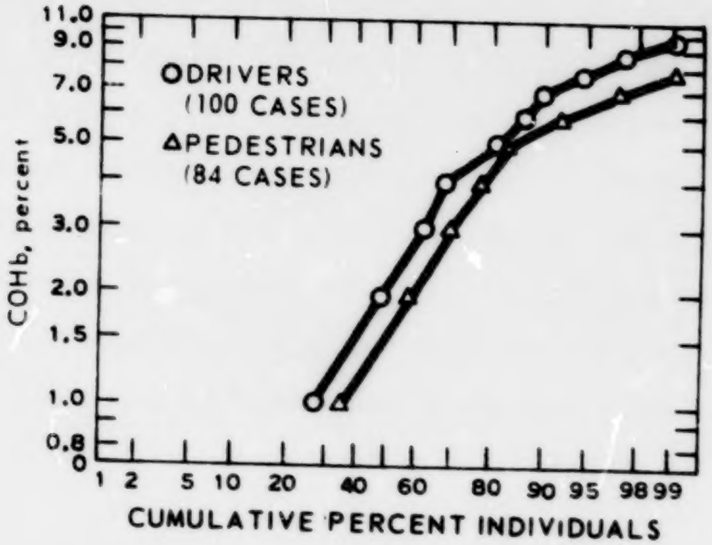

Figure 8-3. Distribution of carboxyhemoglobin among individuals involved in traffic accidents (24).

Chovin (25) studied 331 traffic policemen in Paris. Determinations of COHb were made before and after a 5-hour work period with average CO exposures of 12 to 14 mg/m^3 (10 to 12 ppm). Cigarette smokers who started work with relatively high COHb levels but did not smoke while at work tended to excrete CO, whereas similar smokers who started work with low levels tended to have an increase in COHb. Those who had COHb levels of 3 to 8 percent at the beginning of the work shift showed very little change (Figure 8-4). Nonsmokers had an increase in COHb that was related to the ambient exposure at the intersection where they were directing traffic (Figure 8-5).

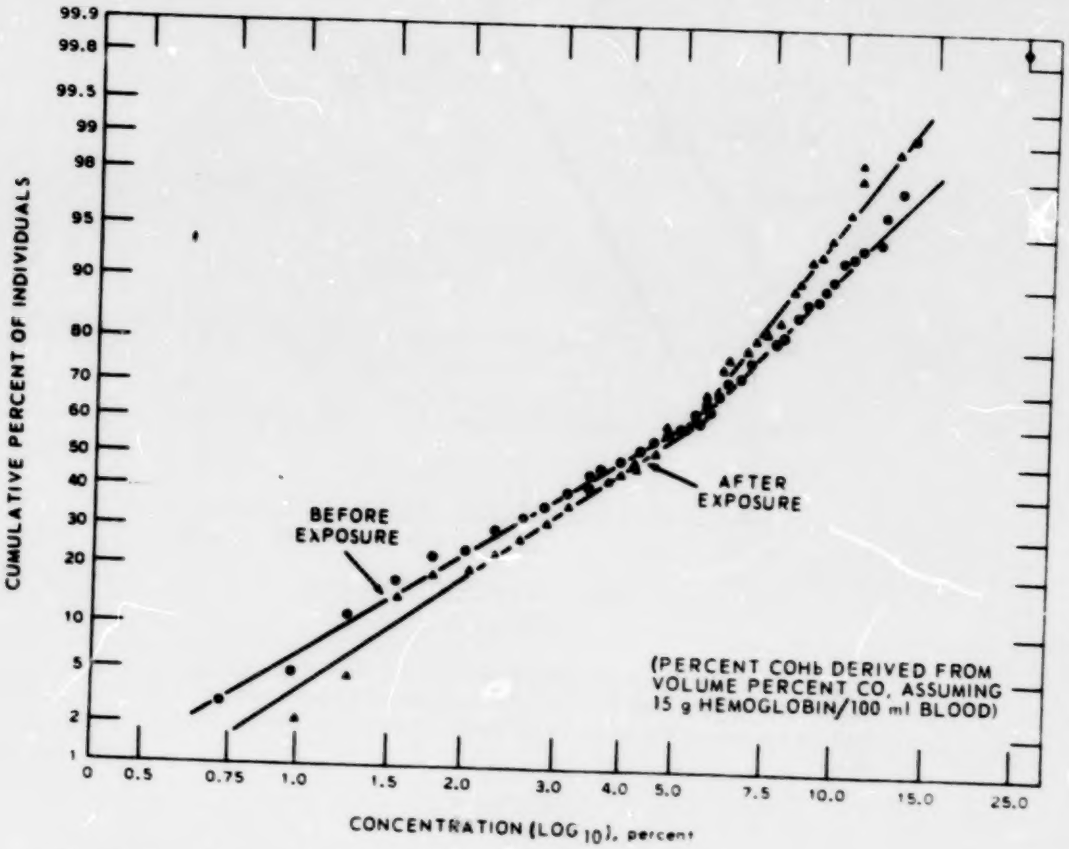

Figure 8-4. Carboxyhemoglobin levels of policemen who smoke before and 5 hours after exposure to between 12 and 23 mg/m^3 (10 and 12 ppm) carbon monoxide, Paris, 1963 (25).

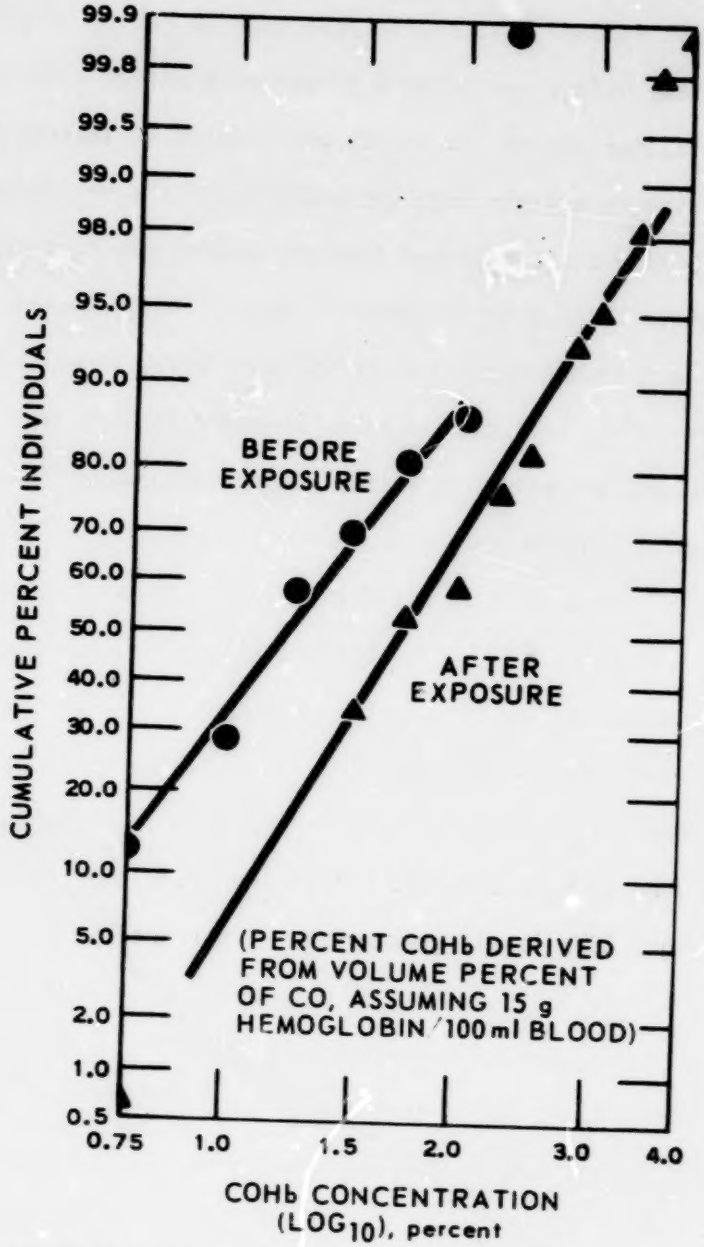

Figure 8-5. Carboxyhemoglobin levels of policemen who do not smoke before and 5 hours after exposure to between 12 and 23 mg/m^3 (10 and 12 ppm) carbon monoxide, Paris, 1963 (25).

Chovin derived the equation:

$$I_{CO} = 0.024C-0.07$$

to depict the manner in which blood CO equilibrium is approached after a person is exposed to traffic for 5 hours. I_{CO} is the increase in blood CO (in cc of CO/100 cc blood), and C is the average ambient CO concentration (ppm). This equation can be expressed in terms of change in percent COHb as follows:

$$\Delta\%COHb = 0.096C - 0.28$$

Thus, for example, an average 5-hour exposure to 22 mg/m^3 (20 ppm) CO would result in an increase of COHb of 1.64 percent, and a 5-hour exposure to 12 mg/m^3 would result in an increase of COHb of about 0.7 percent.

Breysse (26) has conducted a study to determine potential health hazards associated with use of gasoline engine operated fork lift trucks in the holds of ships. Carbon monoxide was determined from expired air samples before work, before lunch, after lunch, and after work. Smoking was noted to have a marked effect upon COHb content. Six percent of nonsmokers had COHb levels greater than 3 percent, and 47 percent of 108 smokers exceeded this level prior to work (Table 8-4). It was further noted that 6 percent of individuals had COHb levels exceeding 10 percent COHb prior to work, and 10 percent exceeded this level after work. No distinction between smokers and nonsmokers was made in this part of the study.

Airplane pilots flying over forest fires have been studied to determine whether CO exposure significantly affected their COHb (5). Expired-air analyses indicated that the blood COHb levels averaged 4.5 percent, reaching a maximum of 8.1 percent in one particular pilot. Again, smoking resulted in a higher range of COHb concentrations than occupation did.

Table 8-4. COHb LEVELS OF 108 SMOKERS AND 92 NONSMOKERS BEFORE WORK (26)

	Nonsmokers			Smokers		
COHb level, percent	Number	Percent	Cumulative percent	Number	Percent	Cumulative percent
0	26	28	28	3	3	3
1	35	38	66	13	12	15
2	21	23	89	21	19	34
3	4	5	94	20	19	53
4	2	2	96	9	8	61
5	2	2	98	10	9	70
6	2	2	100	18	17	87
7	0	0	100	6	6	93
> 7	0	0	100	8	7	100

On the basis of several studies, then, it has been demonstrated that continuous exposure to relatively low levels of CO may result in significant increases in blood COHb levels, for exposure periods as short as 5 hours. Cigarette smoking alone can result in similar or greater increases in COHb levels, and smoking and exposure to ambient levels of CO may both contribute to increasing COHb levels.

3. Cigarette, Pipe, and Cigar Smoke

Carbon monoxide occurs in high concentrations in cigarette smoke (greater than 22,400 mg/m^3; 20,000 ppm; or 2 percent), and the average concentration inhaled is about 460 to 575 mg/m^3 (400 to 500 ppm, or 0.04 to 0.05 percent).

The magnitude of smoking exposures has been estimated in a population of longshoremen examined prior to the work shift and during periods of little community air pollution (5). Exposure estimates were based on measurements of CO in expired air after 20-second breathholding. These estimates were validated by measurement of COHb in a sample of the participants. The results are shown in Table 8-5. A level of 5.9 percent COHb was found to be the median value in moderate cigarette smokers who inhale. The relatively low levels in pipe smokers and cigar smokers are the result of only small amounts of smoke being inhaled when tobacco is consumed in these forms. The effect of inhaling is clearly an increase in the uptake of CO.

Table 8-5. PROPORTION OF SMOKERS AND MEDIAN VALUES OF EXPIRED CO AMONG LONGSHOREMEN (5)

Smoking pattern	Percent of study population by smoking pattern		Median CO, ppm		Median COHb level[a], %	
Never smoked	23.1	(764)[b]	3.2		1.3	
Ex-smoker	12.1	(401)	3.9		1.4	
Pipe and/or cigar smoker only	13.4	(445)	5.4		1.7	
			Inhaler	Noninhaler	Inhaler	Noninhaler
Light smoker (half pack or less per day)	13.0	(429)	17.1	9.0	3.8	2.3
Moderate smoker (more than 1/2 pack and less than 2 packs per day)	31.3	(1,035)	27.5	14.4	5.9	3.4
Heavy smoker (2 packs or more per day)	7.0	(233)	32.4	25.2	6.9	5.5

[a] The percent COHb was estimated from regression.

[b] The number of subjects is given in parentheses. The smoking pattern of four persons was not ascertained.

Ringold et al. (6) have measured concentrations of CO in expired air and grouped their data according to smoking history. As is shown in Figure 8-6, the amount of CO expired is quite clearly related to smoking habits.

C. DEFINITION OF SENSITIVE GROUPS

The concept of a "susceptible population" merits consideration in the study of air pollution epidemiology. Human responses to community air pollution have shown wide variations, which contribute in no small way to the difficulty in assessing the effects of pollutants. Since air quality criteria must, unless otherwise specified, consider all of the population rather than just major segments of it, studies must consider especially the impact of air pollution on the "most sensitive" responders. The

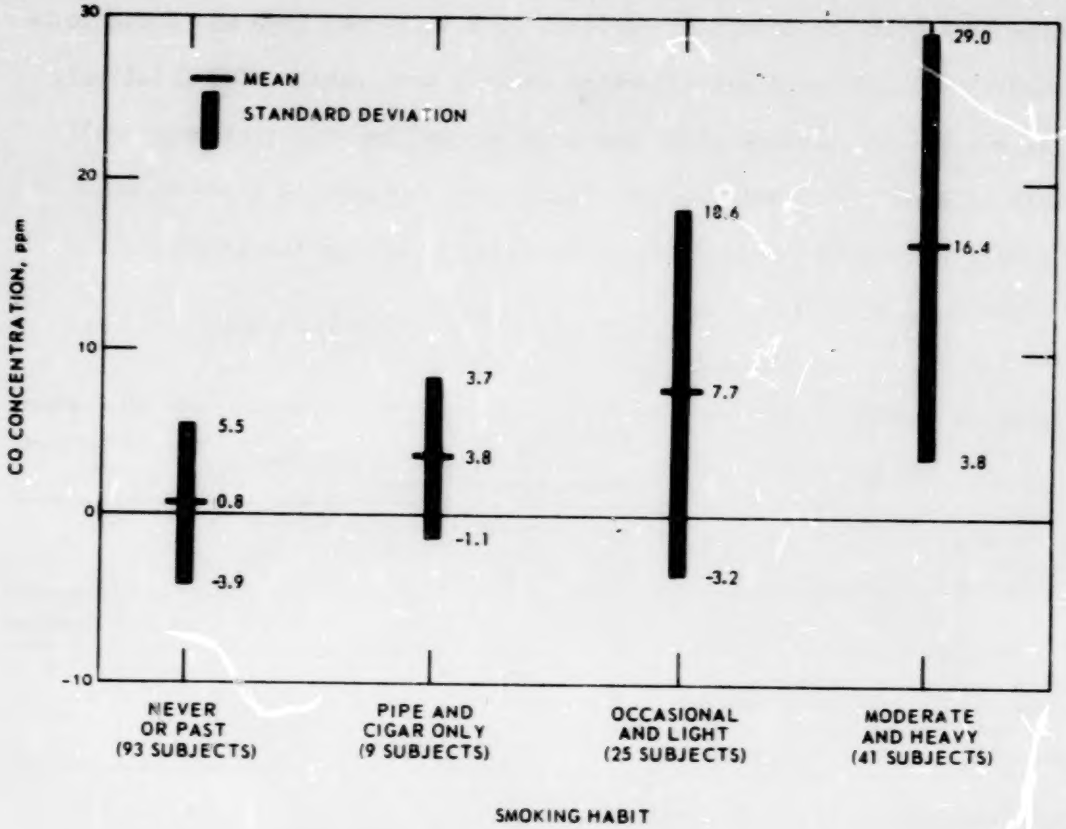

Figure 8–6. Distribution of expired–air carbon monoxide, according to smoking history, and corrected for ambient–air carbon monoxide (6).

population group most susceptible to the adverse effects of atmospheric CO can be predicted on a physiological basis to include those persons most sensitive to a decrease in oxygen supply such as: people with severe anemia because of an already limited supply of oxygen-carrying hemoglobin; those with cardiovascular disease and the resultant impairment of circulation; those with abnormal metabolic states such as thyrotoxicosis or fever, which result in increased oxygen demands; those with chronic pulmonary disease; and the developing fetus, which may be unusually sensitive to insufficient oxygen. Several recent reviews of the pathophysiology of CO exposure include overviews of the population at greatest risk from such exposure (27-29). A recent review of animal and human studies strengthens the impression that, in patients with insufficient arterial blood flow, small amounts of COHb impair unloading of oxygen and further affect the clinical course of insufficiency (30).

In addition to the groups proposed as most sensitive, individuals requiring maximal judgmental and functional ability may be an important group to consider in the discussion of health effects associated with CO. Automobile drivers are the largest group of individuals in this category.

A number of studies have pointed out that cigarette smoking may have a deleterious effect upon the fetus, most notably manifest in an increased incidence of low birth weights and a lower average birth weight, but the usual emphasis has been upon tobacco smoke components other than CO. Haddon (31) has shown that COHb levels in maternal blood are reflected in the cord blood at delivery. The cord blood of infants delivered from cigarette smoking mothers has a higher COHb level than is found in that of infants from nonsmoking mothers. There appears to be a similar level of COHb in maternal and cord blood (Figure 8-7). Whether this in itself results in any other effect on the fetus is at this time uncertain, but unborn infants, who during parturition may have exceptional requirements for oxygenation, may well be among the population at high risk.

D. STUDIES AND INTERPRETATION

1. Mortality Studies

Statistical approaches utilized in determining whether there is excess mortality from atmospheric pollution have been presented by a number of investigators (32-34). Such variables as the concentration of particulates, oxides of sulfur, and oxidants and smoke-shade index have

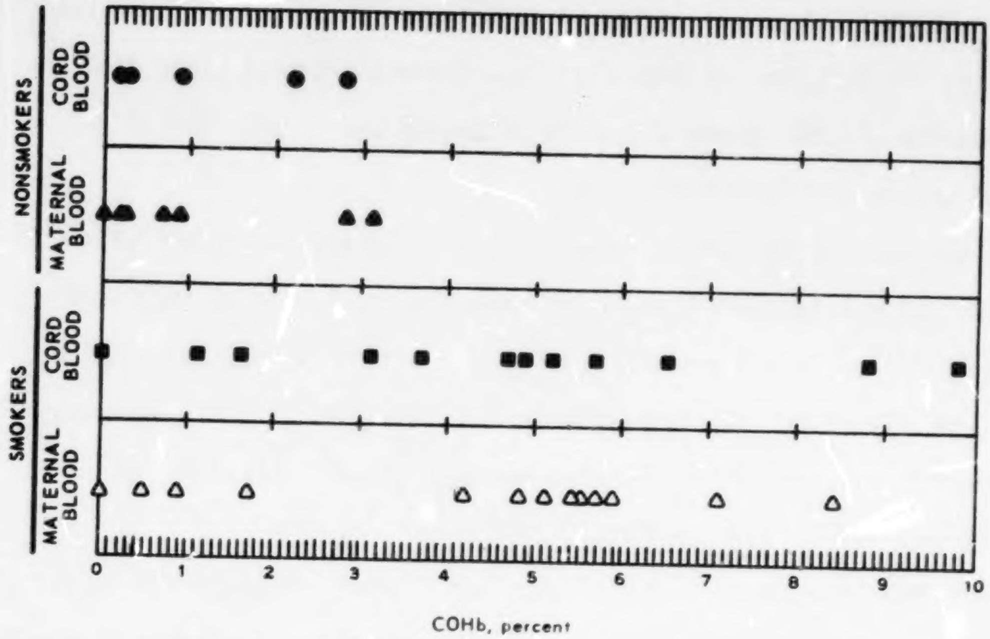

Figure 8-7. Percentage of hemoglobin saturated with carbon monoxide in cord and maternal blood specimens of smokers and nonsmokers (31).

been compared with mortality with some frequency, but CO has not. This may be caused in part by the fact that CO measurements are not always available.

Massey et al. (35) compared mortality in two "communities" in Los Angeles County, which experienced similar daily temperature but different levels of air pollution. The pollutants studied were oxidants, SO_2, and CO. The investigators had to compare areas of intermediate and relatively high pollution rather than low versus high areas because it was not possible to maximize differences in air pollution exposure and still remain within an area of uniform temperature. Differences in daily mortality were analyzed by means of correlation and multiple-regression techniques. There were no significant correlations between mortality and pollutant levels. Another problem involved in this use of spatial analysis was the different characteristics of the populations residing within each area. The populations of the communities differed in median age, sex ratio, social status, urbanization, and racial composition. It was hoped in conducting the two-community study that the daily differences between mortality in the low and high area would be relatively independent from day to day. Previous studies have indicated that the effects that must be taken into account in time-series analyses are those of autocorrelation as well as cyclic seasonal variations. The negative results of this study must be viewed in light of these limitations.

Using data on cardiac and respiratory mortality for 1956, 1957, and 1958, Hechter and Goldsmith (36) have shown that the number of deaths per day in Los Angeles County varies between 1.0 and 1.3 per 100,000 population. These fluctuations were approximately 180 degrees out of phase with fluctuations for maximal daily temperature and oxidant values, and approximately in phase with CO maxima (Figure 8-8). If not properly dealt with, such phase differences can produce spurious correlations. When Fourier curves were fitted to the data,* it was found that a single cycle of Fourier functions fit temperature and oxidant levels, and that two-component Fourier curves fit CO levels and cardiorespiratory mortality (Figure 8-9).

When the residuals from these fitted curves were analyzed, no significant correlations between pollutants and mortality were found (residuals are presumed to have removed the major effect of time of year). In addition, there were no significant correlations when lag periods of 1 to 4 days were utilized in the analysis. It is possible, however, that in an attempt to remove a time-of-year effect, a real

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*Fourier curve-fitting consists of adding successive pairs of sine and cosine functions as variables, each successive pair being functions of twice the angle of the preceding pair.

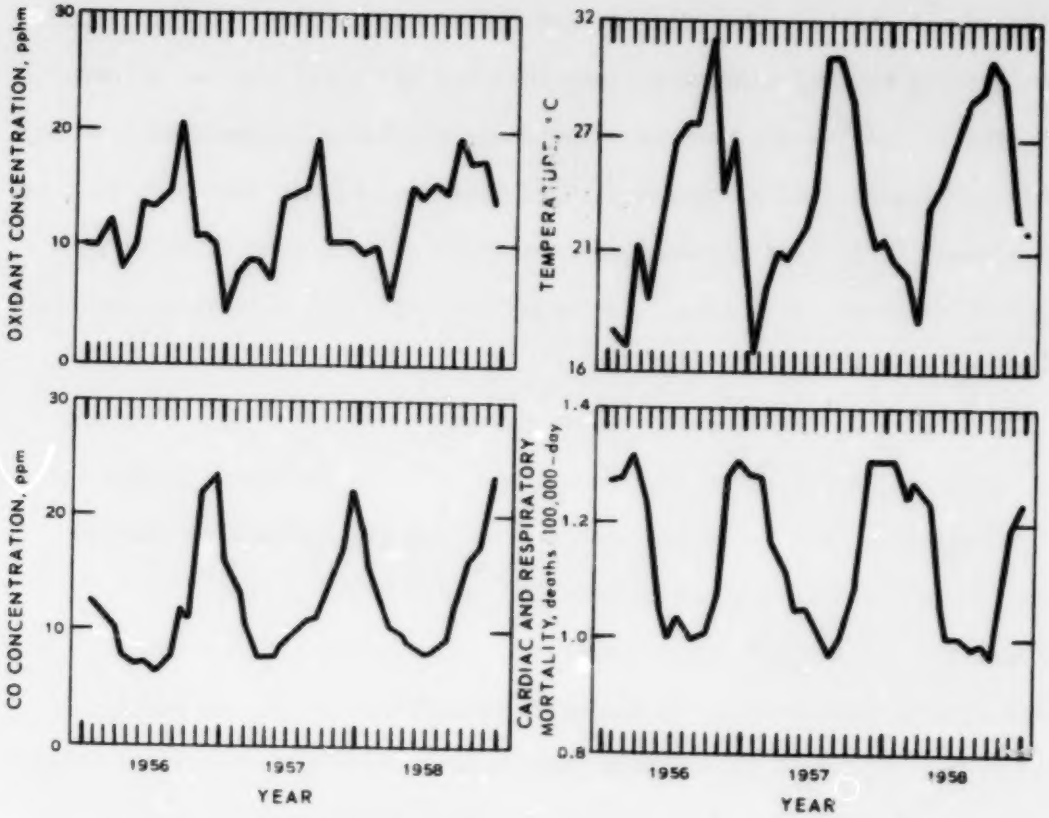

Figure 8-8. Comparison of maximum concentrations of oxidant and carbon monoxide, maximum temperature, and daily death rate for cardiac and respiratory causes, Los Angeles County, 1956-1958 (36).

effect of pollutants on mortality may also have been removed, particularly if it was a small effect.

Curphey et al. (37) attempted to determine whether there is any association between the amount of COHb in postmortem blood and ambient CO levels with the 24-hour period preceding death. The investigators were aware of the possibility that postmortem blood specimens may deteriorate and produce falsely high COHb levels, but they did not find that the length of the interval between death and analysis had any effect on COHb levels in this study.

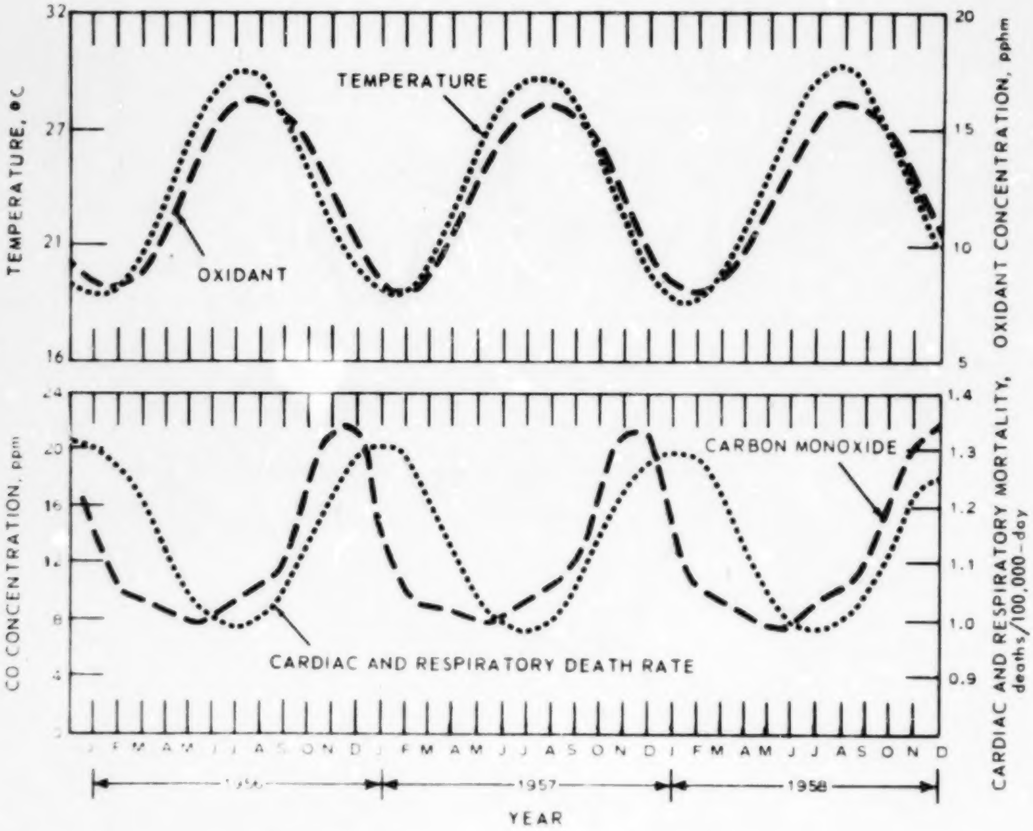

Figure 8-9. Fourier curves fitted to data in Figure 8-8 (15).

Information concerning smoking habits was obtained from a questionnaire mailed to next of kin. A total of 1075 cases for which a COHb determination had been performed were then classified by smoking habits. Nonsmokers consistently had lower COHb levels than smokers. Male nonsmokers had higher COHb levels than female nonsmokers. Variables such as age, time of day and day of week of death, maximum and minimum temperatures, and cause of death had little relationship to COHb levels. There did, however, appear to be some association between ambient CO levels and postmortem COHb levels (Figure 8-10).

These data have been analyzed further in an attempt to determine whether individuals with cardiovascular disease certified by the

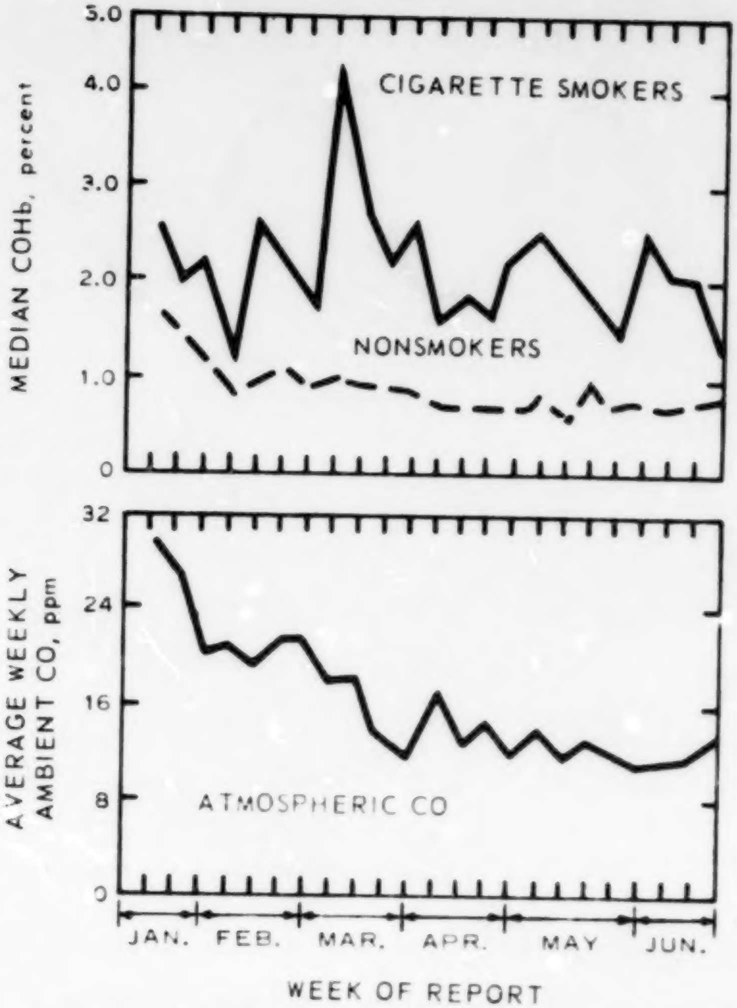

Figure 8-10. Carboxyhemoglobin levels of coroner's cases, by smoking status and atmospheric carbon monoxide concentrations, Los Angeles County, 1961 (37).

coroner's office as having "myocardial infarctions" have different COHb levels than individuals dying of "other cardiovascular disease" (38). Both smokers and nonsmokers were examined initially (Figure 8-11). The myocardial infarction cases were noted to be younger than those dying of "other cardiovascular disease." Since COHb levels of smokers may diminish with age (either associated with the manner in which cigarettes

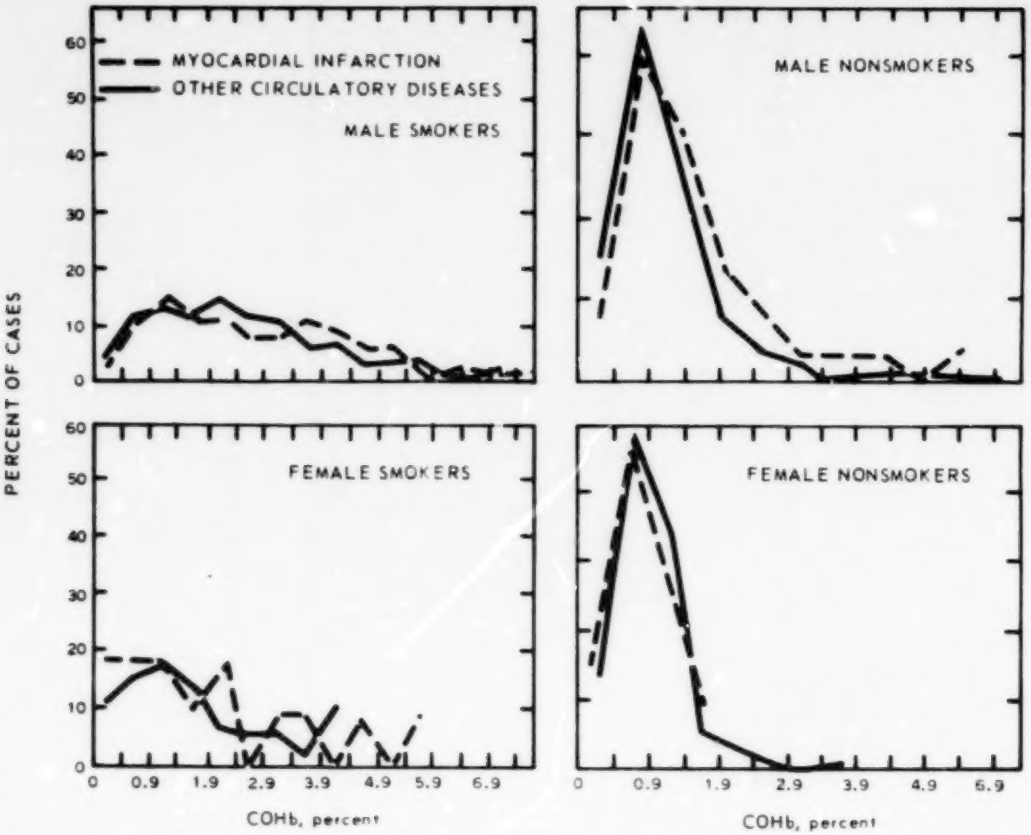

Figure 8–11. Carboxyhemoglobin levels in myocardial infarction deaths and in other cardiovascular disease deaths, Los Angeles County, 1961 (38).

are inhaled or some other factor that interferes with the alveolar diffusion of CO), an adjustment for age is required when comparisons such as these are carried out. When the population was divided into two groups, those 65 and older and those under 65, no significant differences in COHb levels were noted between the two diagnostic categories (Table 8-6). In the male population under age 65, however, the myocardial infarction cases had on the average a higher COHb; but the difference was not significant.

Cohen et al. (39) have attempted to test the hypothesis that during periods of high CO pollution, individuals hospitalized with acute cardiovascular

Table 8-6. COHb LEVELS FOR CARDIOVASCULAR DISEASE CATEGORIES BY AGE, SMOKING HABITS, AND SEX,[a] LOS ANGELES COUNTY, 1961 (38)

Age group and cause of death	Smoker						Nonsmoker					
	Male			Female			Male			Female		
	Mean COHb	S D	Number of cases	Mean COHb	S D	Number of cases	Mean COHb	S D	Number of cases	Mean COHb	S D	Number of cases
Under 65 years												
Myocardial infarction	3.13	1.70	76	(2.10)[b]	1.84	8	1.44	1.30	14	(0.70)[b]	0.22	5
Other circulatory	2.84	1.52	116	3.01	2.43	24	1.15	0.83	45	0.76	0.40	27
65 and older												
Myocardial infarction	1.29	0.64	15	(2.23)[b]	2.81	3	1.18	0.86	23	0.91	0.50	15
Other circulatory	2.02	1.40	80	1.43	1.09	26	0.98	0.69	154	0.92	0.52	194

[a] None of differences within sex, age, and smoking category are statistically significant.

[b] Parentheses indicate mean based on samples smaller than 10 cases.

disease are adversely affected. They have studied myocardial infarction admissions to 35 hospitals in Los Angeles County during 1958. Hospital records were abstracted by the medical librarian staff at each hospital. Information obtained included age, sex, date of admission, date of discharge, discharge diagnosis, disposition of patient (recovery or death), area of residence, area of employment, number of days hospitalized, and date of onset of illness. The analysis included 3080 admissions for myocardial infarction, and involved separate calculations for hospitals in areas of high and low CO pollution.

No significant association was found between the number of admissions for myocardial infarction and ambient CO levels. Significant correlations were found, however, for weekly myocardial infarction case fatality rates and ambient CO levels during the week of admission. Patients admitted to hospitals in the areas of "high" CO pollution where the weekly CO concentration ranged from about 9 to 16 mg/m^3 (8 to 14 ppm) exhibited statistically significant increases ($p<0.01$) in mortality rates from myocardial infarction when compared to patients admitted during weeks with lower average CO concentrations. This correlation was principally accounted for by an end-of-the-year increase in both case fatality rates and ambient CO levels. To avoid spurious correlations, which can result from day-of-week effects as well as autocorrelation, separate analyses were performed for each day of the week and by high and low pollution areas (Table 8-7). Significant associations were then observed only for some of the days of the week and only in the area of the county designated as having high CO levels. The case fatality rates in the high CO area were particularly different from those in the low CO area during weeks of the

Table 8-7. RELATIONSHIP BETWEEN NUMBER OF HOSPITAL ADMISSIONS FOR MYOCARDIAL INFARCTION, MYOCARDIAL INFARCTION CASE FATALITY RATES, AND AMBIENT CO LEVELS BY DAY OF WEEK, LOS ANGELES COUNTY, 1958 (39)

Day of admission	Avg CO concentration, ppm	Total area				High area		Low area	
		Mean myocardial infarction admissions	Correlation[a] coefficient-admissions versus CO	Mean case fatality rate per 100 admissions	Correlation[b] coefficient-case fatality rate versus CO	Mean case fatality rate per 100 admissions	Correlation[a] coefficient-case fatality rate versus CO	Mean case fatality rate per 100 admissions	Correlation[a] coefficient-case fatality rate versus CO
All days	7.41	8.46	0.002	26.0	0.114[c]	27.3	0.162[d]	19.1	-0.002
Weekdays	7.66	8.94	-0.120	24.7	0.130[c]	25.8	0.167[d]	18.4	0.048
Weekends	6.80	7.26	-0.022	30.2	0.177	31.7	0.256[d]	22.0	-0.101
Sunday	6.53	6.94	-0.251	28.3	0.049	29.3	0.037	22.8	0.011
Monday	7.71	9.54	-0.234	25.4	0.019	26.3	0.058	11.7	0.093
Tuesday	7.45	9.41	-0.071	23.5	0.134	24.5	0.096	21.8	0.209
Wednesday	7.53	9.13	0.150	24.2	0.273[c]	24.7	0.186	24.1	0.207
Thursday	7.71	8.08	-0.019	26.9	-0.030	29.4	0.210	18.4	0.161
Friday	7.90	8.56	0.121	23.6	0.262	24.3	0.308[c]	23.5	-0.111
Saturday	7.07	7.58	-0.040	32.0	0.309[c]	34.0	0.466[c]	21.2	-0.182

[a] Correlation between myocardial infarction admissions and log CO (basin average).

[b] Correlation between arc sin transformation of myocardial infarction case fatality rate ($x^1 = \text{arc sin} \sqrt{\frac{x+1}{N+1}} + \text{arc sin} \sqrt{\frac{x}{N+1}}$) where x is the number of deaths and N is the number of admissions and log CO (basin average).

[c] Significant at the 5% level.

[d] Significant at the 1% level.

year with the greatest mean CO levels. The comparability of these two areas was not documented with regard to socioeconomic characteristics.

Factors other than CO exposure, such as hospital admission and hospital care practices and, most important, seasonal influences on case fatality rates, may have accounted for the observed associations. At present, it appears that an association could exist between myocardial infarction case fatality rate and atmospheric CO pollution, but additional studies, particularly of COHb levels in myocardial infarction patients at the time of admission, are required if conclusions are to be drawn about causality. Individuals dying a sudden death, and hospitalized myocardial infarction patients must be examined to determine whether the COHb levels of these two populations differ.

2. Morbidity Studies

There have been few studies in which an attempt has been made to relate community CO exposures to indices of health. Instead, the approach utilized has been to study occupationally exposed groups. Because of the limitations of generalizing from occupational groups to the general population, as previously discussed, community morbidity studies are becoming increasingly important.

Cassell et al. (40) obtained daily records of illness prevalence from a panel of 1747 persons living within a restricted geographic area of New York City. The subjects were followed at weekly intervals for an average of 45 weeks each, providing 61,000 person-weeks of information. Symptoms recorded were common cold, cough, headache, and eye irritation. Pollutants under study included particulate matter, total hydrocarbons, CO, and sulfur dioxide. Meteorologic factors such as wind speed, precipitation, and temperature were also considered. Correlation analyses demonstrated two distinct clusters of environmental variables and their associated symptoms. Headache and eye irritation tended to occur with warm, humid weather and stagnant meteorologic conditions in which there were high levels of CO, ammonia, aldehydes, total oxidants, and organic acids, but low levels of hydrocarbons and sulfur dioxide. The second cluster of effects (common cold, cough, and sore throat) were thought to occur in wintry weather (low solar radiation, low humidity, low temperature, and medium winds) accompanied by high levels of particulate matter and oxides of sulfur, but virtually no oxidant or aldehydes. The relevance of this work to actual effects of CO is limited since the presence of CO was probably only an index of a variety of other pollutants. The association of headache and increased ambient CO concentrations is, however, quite plausible.

Sterling et al. (3,4) assembled Blue Cross admissions data from Los Angeles hospitals for the period March to October 1961. Diagnoses were grouped according to what the authors consider "highly relevant," "relevant," and "nonrelevant" illnesses. After correcting for day-of-week effects in both pollutant and admission frequencies, a statistically significant correlation was found with CO and several other pollutants for "highly relevant" conditions such as allergic disorders, inflammatory diseases of the eye, acute upper respiratory infections, influenza, and bronchitis. Since there is no biologically plausible explanation for such an association, at the present time such a relationship cannot be regarded as significant in terms of CO.

Verma et al. (41) undertook a retrospective study of absences caused by illness among a group of white-collar workers located in metropolitan New York during a 3-year period. Any employee who had been absent because of illness reported to the company medical department for appraisal prior to his returning to work. These records were then categorized as either respiratory or nonrespiratory illness. An association was noted between respiratory illness and ambient sulfur dioxide levels. No such association was observed between respiratory illness and CO, nor was any association found between nonrespiratory illness and sulfur dioxide, smoke shade, or CO. When time trends were removed from the data and the analyses were repeated, there were no significant associations between absences and any of the pollution variables. These data therefore demonstrate yearly cyclic behavior, which tends to influence both pollutants and illness absences. The authors state that the models they developed retain their descriptive power for respiratory illness absences, and suggest that while no causal association can be inferred, there is a relationship between respiratory illness absences, air pollution, and climatic variables from one time period to the next.

3. Possible Relevance of Carbon Monoxide Exposure to Motor Vehicle Accidents

As noted in the prior section dealing with magnitude and type of exposure, motor vehicles contribute a large proportion of community CO pollutic The effects of CO on visual threshold and the ability to discriminate time intervals (42,43) have been discussed in detail in Chapter 7. In view of the increasing evidence that sensory impairment is associated with relatively low-level CO exposures, it has become quite pertinent to determine whether such effects in motor vehicle drivers predispose them to accidents. McFarland (44,45) has reviewed the numerous factors that must be taken into account in epidemiologic studies of motor vehicle accidents.

During the period 1959 through 1963, Chovin (25) determined COHb levels in three population groups. He analyzed 1672 blood samples from motor vehicle drivers who were thought to be responsible for accidents; 3818 samples from workers who were sometimes exposed to CO in their occupations; and 1518 samples from individuals who were suspected of having been exposed to domestic sources of CO. Alcohol measurements were also made on those thought responsible for accidents, but data are not available. The cumulative distribution of blood CO levels is shown in Figure 8-12. Individuals involved in auto accidents had the highest blood CO levels, followed by workers with CO exposure; individuals with suspected exposure to CO in the home had the lowest blood CO levels. Chovin noted that smokers and nonsmokers were present in all three categories, but presented no data to indicate whether the proportion of smokers and nonsmokers is the same in these categories. Other questions, especially the association of increased cigarette consumption with other variables, must be dealt with before any firm conclusions can be drawn from this study.

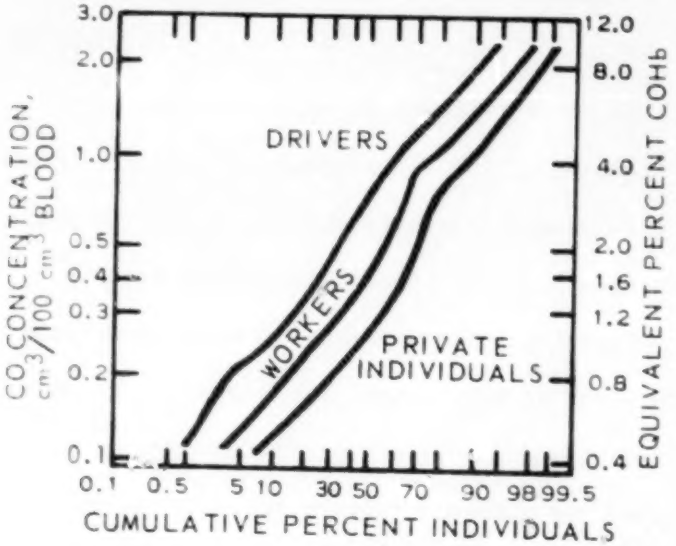

Figure 8-12. Cumulative distribution of blood carbon monoxide concentrations, based on 5-year study of car drivers workmen with carbon monoxide exposure, and private individuals suspected of accidental carbon monoxide exposure (25).

Ramsey (46) studied thirty young, healthy, nonsmoking drivers and 30 older, presumably hypoxic, nonsmoking drivers exposed to an average of 43.8 mg/m^3 (38.1 ppm) of carbon monoxide during 90 minutes of commuting traffic. These groups showed an average of 0.49 and 1.14 volume-percent reduction in oxygen of capillary blood, respectively. A control group of 30 averaged a 0.04 volume-percent reduction. Correlation of CO exposure with O_2 reduction was highly significant. In both groups, 27 of the 30 drivers reacted more slowly to a visual stimulus after being in traffic. The control group had 3.5 percent faster reaction time the second time tested. The correlation between O_2 reduction and time slowing was significant. The hypoxic drivers had significantly less O_2 and had significantly slower reaction times at the beginning than the normal drivers.

Of possible assistance in determining the relevance of CO to automobile accidents would be a study correlating frequency of motor vehicle accidents with temporal and spatial differences in CO levels. A statistical and epidemiological strategy for this purpose has been developed and utilized by Ury (47) for studying the effects of oxidants on automobile accidents.

E. SUMMARY

Exposures to environmental levels of CO can increase blood COHb concentrations in human subjects. The amount of this increase is reasonably predictable and must be considered in relation to CO exposures from inhaled cigarette smoke and from occupational and domestic sources. Methods for estimating COHb levels in large populations are relatively simple.

Continuous exposure to relatively low levels of CO may result in significant increases in blood COHb levels over exposure periods of only a few hours. Such an exposure increases the body burden of COHb in persons who do not already have such a body burden from cigarette smoking. Longer exposures would most likely produce a somewhat greater increase, with greater potential for impairment of tissue oxygenation.

Exposure of traffic policemen, in Paris, for 5 hours to 12 to 14 mg/m^3 (10 and 12 ppm) increased COHb levels in nonsmokers by about 0.7 percent. The same exposures of cigarette smokers may cause those who have elevated COHb at the start of exposure to have a decrease in COHb and those who had relatively low values of COHb at the start of the study to have an increase in COHb. Cigarette smoking was not permitted during this 5-hour period of exposure.

Apart from increases in COHb, four possible effects have been a source of major consideration in epidemiologic studies:

1. Continued exposure to low levels of CO may produce some persistent toxic reaction, such as a chronic CO poisoning syndrome. The evidence for the occurrence of such a condition is inadequate and is based primarily on subjective symptoms.
2. Data suggest that weekly average CO values in excess of 9 to 16 mg/m^3 (8 to 14 ppm) may be associated with an increase in mortality in hospitalized patients with myocardial infarction. Substantiation of this impression will require a study of the prognosis of myocardial infarction patients in relationship to COHb levels measured at admission to the hospital.
3. It appears that drivers in commuting traffic undergo temporary reduction in blood O_2 content. Whether this amount of O_2 reduction results in refined, subtle impairment of the central

nervous system is difficult to conclude, but there is suggestion that in some cases it may. It appears that driving in commuting traffic ordinarily offers very little health hazard or accident risk to a young, healthy, nonsmoking driver. This may not be so for older, hypoxic drivers. In one study, 30 such drivers after 9 minutes in the same traffic had 3.06 volume-percent less O_2 in capilla blood and had 28.3 percent slower reaction time than 30 young, healthy drivers; thus, older, hypoxic drivers may be potential accident risks. The difference of 100 msec in reaction time may make the difference between safety and mishap. When smoking is considered, such conclusions are further strengthened.

4. In two studies, persons driving motor vehicles that were involved in accidents had higher COHb levels than "control" populations: controls were not ideal, however. Possible mechanisms by which CO might affect the ability to drive a motor vehicle are suggested in the available data on CO effects upon visual sensitivity, psychological test performance, and accurate estimation of time intervals. As little as 2.5 percent COHb has produced these effects in laboratory studies of nonsmokers, and the available epidemiologic information is consistent with the premise that such an increase in COHb levels among drivers might influence the frequency of accidents.

Specific areas in which research is needed to clarify uncertainties relating to health effects of CO exposure are:

1. The increment of COHb that can be produced by exposures to CO concentrations in the range of 12 to 23 mg/m^3 (10 to 20 ppm) for time periods of 8 to 24 hours.

2. The relationship of ambient CO levels and of COHb levels to the survival of hospitalized patients with myocardial infarction.
3. The prognostic significance with respect to cardiovascular conditions of elevated levels of COHb.
4. The relationship, if any, between ambient CO and COHb levels and the occurrence of motor vehicle accidents when weather and driving conditions, cigarette smoking, alcohol and drug use, and other factors are adjusted and controlled.
5. The relationship between concentrations of CO measured outdoors and inside households.

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APPENDIX

CONVERSION BETWEEN VOLUME AND MASS UNITS OF CONCENTRATION

The physical state of gaseous air pollutants at atmospheric concentrations may be described by the ideal gas law:

$$pv = nRT \qquad (1)$$

where:
p = Absolute pressure of gas
v = Volume of gas
n = Number of moles of gas
R = Universal gas constant
T = Absolute temperature

The number of moles (n) may be calculated from the weight of pollutant (w) and its molecular weight (m) by:

$$n = \frac{w}{m} \qquad (2)$$

Substituting equation 2 into equation 1 and rearranging yields:

$$v = \frac{wRT}{pm} \qquad (3)$$

Parts per million refers to the volume of pollutant (v) per million volumes of air (V).

$$ppm = \frac{v}{10^6 V} \qquad (4)$$

Substituting equation (3) into equation (4) yields:

$$ppm = \frac{w}{V}\,\frac{RT}{pm10^6} \qquad (5)$$

Using the appropriate values for variables in equation 5 a conversion from volume to mass units of concentration for CO may be derived as shown below.

T = 298°K (25°C)
p = 1 atm
m = 28 g/mole
R = 8.21×10^{-2} ℓ-atom/mole °K

$$ppm = \frac{w(g) \times 10^3\,(mg/g)}{V(\ell) \times 10^{-3}(m^3/\ell)}\;\frac{8.21 \times 10^{-2}\,(\ell\text{-atm/mole}^\circ K) \times 298(^\circ K)}{1(atm) \times 28\,(g/mole) \times 10^6}$$

$$1\ mg/m^3 = 0.87\ ppm$$
$$1\ ppm = 1.15\ mg/m^3$$

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